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(57) Abstract

A genus of novel peptide analogs which have potent renin-inhibiting activity, methods of treating renin-based hypertension using these compounds, and pharmaceutical compositions containing these compounds as active ingredients.

PEPTIDE ANALOGS

Technical Field

The present invention relates to novel organic compounds which inhibit renin, processes for making such compounds, synthetic intermediates employed in these processes and methods of treating hypertension with such compounds.

Background Art

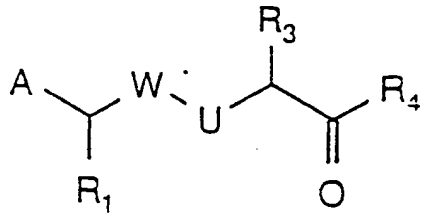
Renin is a proteolytic enzyme synthesized and stored principally in a specific part of the kidney called the juxtaglomerular apparatus. Any of three different physiologic circumstances may cause the release of renin into the circulation: (a) a decrease in the blood pressure entering or within the kidney itself; (b) a decrease in the blood volume in the body; or (c) a fall in the concentration of sodium in the distal tubules of the kidney.

When renin is released into the blood from the kidney, the renin-angiotensin system is activated, leading to vasoconstriction and conservation of sodium, both of which result in increased blood pressure. The renin acts on a circulating protein, angiotensinogen, to cleave out a fragment called angiotensin I (AI). AI itself has only slight pharmacologic activity but, after additional cleavage by a second enzyme, angiotensin converting enzyme (ACE), forms the potent molecule angiotensin II (AII). The major pharmacological effects of AII are vasoconstriction and stimulation of the adrenal cortex to release aldosterone, a hormone which causes sodium retention. AII is cleaved by an aminopeptidase to form angiotensin III (AIII), which compared to AII, is a less potent vasoconstrictor but a more potent inducer of aldosterone release.

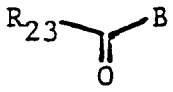
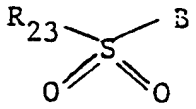
1982) which also cause potent renin inhibition and show a high specificity for this enzyme.

Disclosure of the Invention

In accordance with the present invention, there are renin inhibiting compounds of the formula:



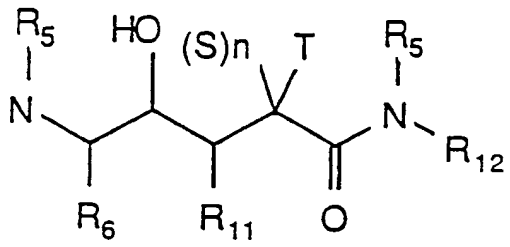
wherein A is hydrogen; loweralkyl; arylalkyl; OR_{20} or SR_{20} wherein R_{20} is hydrogen, loweralkyl or aminoalkyl; $NR_{21}R_{22}$ wherein R_{21} and R_{22} are independently selected from hydrogen, loweralkyl, aminoalkyl, cyanoalkyl and hydroxyalkyl;

 and 

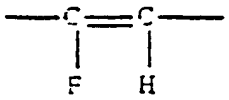
wherein B is NH, alkylamino, S, O, CH_2, $NHCH_2$ or CHOH and R_{23} is loweralkyl, cycloalkyl, aryl, arylalkyl, alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, arylalkoxy, arylalkoxyalkyl, amino, alkylamino, dialkylamino, (hydroxyalkyl)(alkyl)amino, [(dialkylamino)alkyl](alkyl)amino, (dihydroxyalkyl)(alkyl)amino, carboxyalkyl, aminoalkyl, N-protected aminoalkyl, alkylaminoalkyl, alkoxycarbonylalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, (heterocyclic)alkyl or a substituted or unsubstituted heterocyclic;

W is C=O or CHOH;

U is CH_2 or NR_2, provided that when W is CHOH then U is CH_2;



wherein R_5 is hydrogen or loweralkyl; R_6 is loweralkyl, cycloalkylmethyl, benzyl, or CH_2R_{24}, where R_{24} is selected from 1,3-dioxan-2-yl; 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl or 1,3-dithian-2-yl; R_7, R_8 and R_9 are hydrogen or loweralkyl and may be the same or different; V is NH, O, S, SO, SO_2, or CH_2; R_{10} is loweralkyl, cycloalkyl, cycloalkyl-alkyl, aryl, arylalkyl or an N-protecting group, or V and R_{10} taken together are N_3; with the proviso that R_{10} may be an N-protecting group only when V is NH; R_{13} is CHOH or CO; R_{14} is CH_2, CF_2 or CF with the proviso that when R_{13} is CO, R_{14} is CF_2; R_{15} is CH_2, CHR_{25} wherein R_{25} is loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, or R_{14} and R_{15} taken together can be



with the proviso that when R_{14} is CF_2, R_{15} is CH_2; M is O, S, SO, SO_2, NR_{26} wherein R_{26} is hydrogen or loweralkyl, $NR_{27}SO_2$ or $NR_{27}CO$ wherein R_{27} is hydrogen or loweralkyl, or M and R_{10} taken together are N_3; R_{16} is CH_2, CF_2 or CHR_{45} where R_{45} is loweralkyl, hydroxy, hydroxyalkyl,

The term "arylalkyl" as used herein refers to an unsubstituted or substituted aromatic ring appended to an alkyl radical including but not limited to benzyl, 1- and 2-naphthylmethyl, halobenzyl and alkoxybenzyl.

The term "alkylamino" as used herein refers to a loweralkkyl radical appended to an NH radical.

The term "cycloalkyl" as used herein refers to an aliphatic ring having 4 to 7 carbon atoms.

The term "cycloalkylmethyl" as used herein refers to a cycloalkyl group appended to a methyl radical, including but not limited to cyclohexylmethyl.

The term "aryl" as used herein refers to a substituted or unsubstituted aromatic ring including but not limited to phenyl, naphthyl, halophenyl and alkoxy-phenyl.

The term carboxyalkyl as used herein refers to a carboxylic acid group (-COOH) appended to a loweralkyl radical.

The terms "alkoxy" and "thioalkoxy" as used herein refer to $R_{29}O-$ and $R_{29}S-$, respectively, wherein R_{29} is a loweralkyl group.

The term "arylalkoxy" as used herein refers to an aryl appended to an alkoxy radical.

The term "arylalkoxyalkyl" as used herein refers to an aryalkoxy appended to a loweralkyl radical.

The term "dialkylamino" as used herein refers to $-NR_{30}R_{31}$ wherein R_{30} and R_{31} are independently selected from loweralkyl groups.

The term "N-protected aminoalkyl" as used herein refers to NHR_{32} is appended to a loweralkyl group, where R_{32} is an N-protecting group.

The term "(heterocyclic)alkyl" as used herein refers to a heterocyclic group appended to a loweralkyl radical, including but not limited to imidazoylalkyl.

The term alkoxycarbonylalkyl as used herein refers to $R_{33}C=OR_{34}$, wherein R_{33} is an alkoxy

wherein R_{42} is a loweralkyl group.

The term "(N-protected)(alkyl)aminoalkyl" as used herein refers to $NR_{32}R_{42}$, which is appended to a loweralkyl radical, wherein R_{32} and R_{42} are as defined above.

The term "dialkylaminoalkyl" as used herein refers to $NR_{43}R_{44}$ appended to a loweralkyl radical wherein R_{43} and R_{44} are independently selected from loweralkyl.

The term "(thioalkoxy)alkyl" as used herein refers to thioalkoxy appended to a loweralkyl radical.

The term "aminoalkyl" as used herein refers to $-NH_2$ appended to a loweralkyl radical.

The term "heterocyclic ring" or "heterocyclic" as used herein refers to any 5-, 6-, 9- or 10-membered ring containing from one to three heteroatoms selected from the group consisting of nitrogen, oxygen, and sulfur; having various degrees of unsaturation; wherein the nitrogen and sulfur heteroatoms may optionally be quaternized; and including any bicyclic group in which any of the above heterocyclic rings is fused to a benzene ring. Heterocyclics in which nitrogen is the heteroatom are preferred. Fully saturated heterocyclics are also preferred. Preferred heterocyclics are: pyrryl, pyrrolinyl, pyrrolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, imidazolinyl, imidazolidinyl, pyridyl, piperidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, morpholinyl, thiazolidinyl, thiazolyl, isothiazolyl, isothiazolidinyl, indolyl, quinolinyl, isoquinolinyl, benzimidazolyl, benzothiazolyl, benzoxazolyl, furyl, thienyl and benzothienyl.

Saturated heterocyclics may be unsubtituted or mono- or di-substituted with hydroxy, oxo, amino, alkylamino, dialkylamino or loweralkyl. Unsaturated heterocyclics may be unsubstituted or monosubstituted with hydroxy, amino, alkylamino, dialkylamino or loweralkyl.

term "hydrophilic, amino acid side chain" as used herein refers to those amino acid side chains which have an affinity for water and include but are not limited to, those of serine, threonine, allothreonine, homoserine, cysteine, ornithine, arginine, and glutamine. General reference to amino acid side chains in both the description and claims herein is to be taken as reference to such, whether naturally occurring in protein or not, and to both D- and L-forms.

The term "alkylidene" used herein refers to a straight or branched chain alkyl radical which is attached via a carbon-carbon double bond and includes but is not limited to methylidene, ethylidene, 1-propylidene, 1-butylidene, 1-pentylidene, 2-propylidene, 2-butylidene, 2-pentylidene, 3-pentylidene, 3-hexylidene, 3-heptylidene, and 4-heptylidene.

The term "alkylidene oxide" used herein refers to an epoxide moiety which is derived from an alkylidene group.

The terms "thioalkyl, haloalkyl or azidoalkyl" used herein refer to an alkyl radical which has appended to it a thio, halo or azido radical, respectively.

The terms "Ala", "His", "Leu", "Phe", "Tyr", "Cys", "Gly", "Lys", Sar", "Ser", "Thr" and "Pro" as used herein refer to alanine, histidine, leucine, phenylalanine, tyrosine, cysteine, glycine, lysine, sarcosine, serine, threonine, and proline, respectively.

The following examples will serve to further illustrate preparation of novel compounds of the present invention.

Example 1

(3S,4S)-4-t-Butyloxycarbonylamino-3-hydroxy-6-methyl-1-heptene

To a rapidly stirred -78°C solution of Boc-leucinal (1.5 g, 6.97 mmol) in anhydrous tetrahydrofuran (THF) (10 mL) was added a -78°C solution of vinyl

(6.7 g) in water, (21 mL) was then added followed by careful addition of H_2O_2 (18 mL of 30%). The resulting mixture was heated at 65°C for 1 h, the THF was partially evaporated and the residue was distributed between ethyl acetate and brine solution. The organic phase was washed with brine solution and dried over $MgSO_4$. Evaporation of the solvent gave a residual oil which was flash chromatographed on silica gel eluting with 5% MeOH in methylene chloride. The pure fractions were combined and evaporated to give 4.62 g of 4(S)-isobutyl-5(S)-(2-hydroxyethyl)-2-oxazolidinone. A solution of this material (3.95 g, 0.021 mol) and triethylamine (3.2 g, 0.032 mol) in methylene chloride (40 mL) was cooled to 0°C and treated by dropwise addition with mesyl chloride (2.89 g, 0.025 mol). After stirring for 1 h at 0-5°C, the methylene chloride was washed successively with 0.5 N HCl, aqueous $NaHCO_3$ and brine solution. The organic solution was dried and evaporated to a solid product. Recrystallization from hexane/methylene chloride gave 3.9 g (70%) of product, m.p. 99-100°C.

Anal. calcd. for $C_{10}H_{19}NO_5S$: C, 45.27; H, 7.22; N, 5.28.

Found: C, 45.38; H, 7.18; N, 5.23.

Example 4

4(S)-Isobutyl-5(S)-[2-(phenethylmercapto)ethyl]-2-oxazolidinone

To a 0°C solution of 4(S)-isobutyl-5(S)-(2-mesyloxyethyl)-2-oxazolidinone (500 mg, 1.88 mmol) and phenethyl mercaptan (273 mg, 1.98 mmol) in THF (6 mL) was added NaH (95 mg, 1.98 mmol of a 50% dispersion) all at once. The reaction was stirred for 3 h at room temperature and then distributed between methylene chloride and brine solution. The organic layer was washed with brine solution, dried over $MgSO_4$ and evaporated. The residue was chromatographed on

and evaporated to a solid product. Trituration with hexane/ether (50/50) gave 495 mg (92%) of product, m.p. 100-101°C.

Anal. calcd. for $C_{17}H_{25}NO_4S$: C, 60.15; H, 7.42; N, 4.13.

Found: C, 60.27; H, 7.42; N, 4.00.

Example 9

4(S)-Isobutyl-5(S)-[2-isoamylsulfonyl)ethyl]-2-oxazolidinone

Using the procedure of Example 8 with the resultant compound of Example 5, gave the desired compound, m.p. 87-88°C.

Anal. calcd. for $C_{14}H_{27}NO_4S$: C, 55.05; H, 8.91; N, 4.59.

Found: C, 55.11; H, 9.31; N, 4.61.

Example 10

(3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylmercaptoheptane

A solution of 4(S)-isobutyl-5(S)-[2-(phenethyl-mercapto)ethyl]-2-oxazolidinone (0.52 g, 1.69 mmol) and barium hydroxide octahydrate (1.06 g, 3.38 mmol) in dioxane (60 mL) and water (40 mL) was heated at reflux under N_2 for 21 h. The solid barium carbonate was filtered and the filtrate was partially evaporated. The residue was diluted with water and the resulting solution was extracted with ether. The organic extract was washed with brine solution, dried over $MgSO_4$ and evaporated to a residue. Trituration with cold hexane gave 365 mg (77%) of product, m.p. 95-96°C.

Anal. calcd. for $C_{16}H_{27}NOS$: C, 68.28; H, 9.67; N, 4.98.

Found: C, 67.99; H, 9.66; N, 4.75.

Example 11

(3S,4S)-4-Amino-3-hydroxy-1-isoamylmercapto-6-methylheptane

Using the procedure of Example 10 with the

Example 16

Boc-Phe-Ala Amide of (3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylmercaptoheptane

To a stirred -12°C solution of Boc-Phe-Ala-OH (47.8 mg, 0.142 mmol) in anhyrous tetrahydrofuran (3 mL) were added N-methylmorpholine (15.6 uL, 0.142 mmol) and isobutylchloroformate (18.4 uL, 0.142 mmol) sequentially. After 3 min, a -12°C solution of the resultant compound of Example 10 (0.142 mmol) in anhydrous tetrahydrofuran (2 mL) was added. Ten minutes later, the mixture was allowed to warm to room temperature for 2 h, at which time the solvent was evaporated, and the resulting residue was partitioned between ethyl acetate (20 mL) and saturated $NaHCO_3$ (5 mL). The organic phase was washed sequentially with 0.01 M H_3PO_4 (3 mL) and brine (5 mL). Drying (Na_2SO_4) and evaporating provided 77 mg (90%) of the desired compound as a glass.

Anal. calcd. for $C_{33}H_{49}N_3O_5S$: C, 66.08; H, 8.23; N, 7.00.

Found: C, 66.11; H, 8.35; H, 6.84.

Example 17

Boc-Phe-Ala Amide of (3S,4S)-4-Amino-3-hydroxy-1-isoamylmercapto-6-methylheptane

Using the procedure of Example 16 with the resultant compound of Example 11, gave the desired compound, m.p. 137-138°C.

Anal. calcd. for $C_{30}H_{51}N_3O_5S$: C, 63.68; H, 9.09; N, 7.43.

Found: C, 64.01; H, 8.93; N, 7.39.

Example 18

Boc-Phe-Ala Amide of (3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylsulfonylheptane

Using the procedure of Example 8 with the resultant compound of Example 16, gave the desired compound, m.p. 186-187°C.

residue which was partitioned between ethyl acetate (20 mL) and saturated $NaHCO_3$ (8 mL). The organic phase was then washed separately with saturated $NaHCO_3$ (8 mL) and brine (8 mL). Drying (Na_2SO_4) and evaporating provided a white solid which was chromatographed on SiO_2 (95/5, dichloromethane/ methanol) to give 180 mg (75%) of the desired compound. Mass spectrum: $(M+H)^+ = 664$.

Example 23

Boc-Phe-His Amide of (3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylsulfonylheptane

Using the procedure of Example 22 with the resultant compound of Example 12, gave the desired compound.

Anal. calcd. for $C_{36}H_{51}N_5O_7S$: C, 61.96; H, 7.37; N, 10.03.

Found: C, 61.38; H, 7.71; N, 9.07.

Example 24

(5S,6S)-5-Acetoxy-6-t-butyloxycarbonylamino-8-methyl-1-nonene

Using the procedure of Example 1 but changing vinyl magnesium bromide to butenyl magnesium bromide, gave a 56% yield of (5S,6S)-6-t-butyloxycarbonylamino-5-hydroxy-8-methyl-1-nonene as an oil. A 25 g (0.092 mol) sample of this material was dissolved in methylene chloride (200 mL) containing 10 mL of pyridine. Acetic anhydride (11.74 g, 0.115 mol) was added by dropwise addition and the resulting mixture was stirred for 24 h at room temperature. The mixture was washed successively with aqueous $NaHCO_3$, aqueous citric acid and brine solution. After drying over $MgSO_4$, the solvent was evaporated to a residue. Flash chromatography on silica gel gave an 82% yield of product as an oil.

Anal. calcd. for $C_{17}H_{31}NO_4$: C, 65.15; H, 9.97; N, 4.47.

of the solvent left 10 g of glycolic material as a viscous syrup. The above glycol (10 g, 0.043 mol) was dissolved in 150 mL of water and treated all at once with a solution of periodic acid (9.1 g, 0.04 mol) in 150 mL of water. After stirring at 25°C for 5 h, the mixture was extracted with methylene chloride. The dried methylene chloride solution was evaporated to give a quantitative yield of product.

Example 27

4(S)-Isobutyl-5(S)-(6-methyl-3-oxoheptyl)-2-oxazolidinone

A 2 g (0.01 mol) portion of the compound from Example 26 was dissolved in THF (50 mL) and treated at 0-5°C with 37.5 mL of an 0.8 M solution of isopentyl magnesium bromide in THF. The reaction was stirred for 2 h at room temperature and then poured into ice water which contained 6.5 mL of 6 N HCl. The mixture was extracted with methylene chloride. Evaporation of the dried methylene chloride solution gave a quantitative yield of the Grignard adduct. This material was dissolved in 300 mL of acetone and treated by dropwise addition with Jones solution until the orange color persisted. The chromium salts were filtered and the filtrate was evaporated. The residue was diluted with ether and the resulting solution was washed successively with aqueous $NaHCO_3$ and brine solution. After drying over $MgSO_4$, the solvent was evaporated to give 1.7 g (66%) of product as an oil. NMR (300 MHz, $CDCl_3$, ppm): 0.86-0.96 (m,12H), 2.41 (m,2H), 2.67 (m,2H), 3.5 (m,1H), 4.15 (m,1H).

Example 28

4(S)-Isobutyl-5(S)-(6-methyl-3-oxoheptyl)-2-oxazolidinone Ethylene Ketal

A mixture of the product from Example 27 (2.5 g, 9.3 mmol), ethylene glycol (7.5 mL) and p-toluenesulfonic acid (60 mg) in toluene (100 mL) was

Example 31

Boc-His Amide of (3S,4S)-4-Amino-3-hydroxy-6-methyl-1-phenethylsulfonylheptane

Using the procedure of Example 22 with the resultant compound of Example 12 and Boc-His-OH rather than Boc-Phe-His-OH, gave the desired compound.

Example 32

[(4-Morpholinyl)carbonyl]-Phe Methyl Ester

A suspension of L-phenylalanine methyl ester hydrochloride (6 g) in toluene (125 mL) was heated to 100°C while phosgene gas was bubbled into the reaction mixture. After approximately 1.5-2 h, the mixture became homogeneous. The passage of phosgene was continued for an additional 15 min, keeping the temperature at 90-100°C. The toluene was then evaporated and the residue chased several times with benzene. A 6.5 g (0.03167 mol) sample of -isocyanato-L-phenylalanine methyl ester was dissolved in 50 mL of methylene chloride and cooled to 0°C. Morpholine (2.76 mL, 0.03167 mol) dissolved in 5 mL of methylene chloride was added dropwise. After 10 min at 0-5°C, the reaction mixture was distributed between 0.5 N HCl and methylene chloride. The organic layer was washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent gave 7 g of product after trituration with hexane, m.p. 90-91°C.

Example 33

[(4-Morpholinyl)carbonyl]-Phe-OH

To a 0°C solution of the product from Example 32 (3.63 mmol) in dioxane (15 mL) was added a solution of lithium hydroxide (0.174 g, 4.15 mmol) in water (7.5 mL). After stirring for 1 h at 0-5°C, the reaction mixture was diluted with cold water and extracted 2X with ether. The aqueous portion was acidified with 6N HCl and extracted with ether. The organic extract was washed with brine and evaporated to

Example 36

3-Benzyloxycarbonylamino-3-methylbutanoic Acid

A solution of 2,2-dimethyl-3-carbomethyoxy-propionic acid [LeMaul, Bull. Soc. Chim. Fr., 828 (1965), 20 g, 0.125 mol], diphenylphosphorylazide (34.3 g, 0.125 mol) and triethylamine was heated in toluene (150 mL) at 100°C for 2 h. After cooling to 5°C, the toluene solution was washed successively with 0.5 M HCl, aqueous $NaHCO_3$ and brine. Evaporation of the dried solution gave a residue which was chromatographed on silica gel eluting with 60/40 hexane/ether. There was obtained 13 g of methyl 3-isocyanato-3-methylbutanoate as a mobile liquid. A solution of this material in toluene (20 mL) was treated with benzyl alcohol (13 mL) and the resulting mixture heated at reflux for 40 h. Evaporation of the toluene left a residue which was dissolved in methanol (125 mL) and then treated with a solution of NaOH (6.6 g, 0.165 mol) in 22 mL of water. After 5 h, the reaction mixture was partially evaporated, washed with ether and acidified with 6N HCl. Extraction with methylene chloride and evaporation gave 21 g of the desired product. NMR (300 MHz, $CDCl_3$): 1.42 (s,6H), 2.78 (s,2H), 5.08 (s,2H).

Example 37

Cbz-[(ß,ß-di-Me)-ß-Ala]-Phe-OCH_3

A 4.0 g sample of 3-benzyloxycarbonylamino-3-methylbutanoic acid was coupled to phenylalanine methyl ester hydrochloride (3.43 g) using the mixed anhydride procedure described in Example 16. Purification of the crude product by flash chromatography eluting with 65/35 ether/hexane gave an 86% yield of product. NMR (300 MHz, $CDCl_3$): 1.32 (s,3H), 1.34 (s,3H), 2.46 (d,1H), 2.63 (d,1H), 2.98 (dd,1H), 3.09 (dd,1H), 3.70 (s,3H), 4.86 (dd,1H), 4.97 (d,1H), 5.2 (d,1H), 5.3 (s,1H), 6.13 (d,1H).

was continued for 20 h. Work-up and chromatography gave methyl 3-benzyloxycarbonyl-amino-2,2-dimethylpropionate. NMR (300 MHz, $CDCl_3$): 1.2 (s,6H), 3.3 (d,2H), 3.68 (s,3H), 5.1 (s,2H), 5.22 (m,1H). A sample of the methyl ester (6.21 g, 0.023 mol) was saponified with 3.1 g (0.78 mol) of NaOH in 100 mL ethanol/10 mL H_2O at room temperature for 48 h. Work-up as in Example 36 gave the desired product as a liquid. NMR (300 MHz, $CDCl_3$): 1.23 (s,6H), 3.32 (d,2H), 5.10 (s,2H), 5.27 (m,1H).

Example 42

Cbz-[(α, α-di-Me)-ß-Ala]-(OMe)Tyr-OCH_3

To a solution of 3-benzyloxycarbonylamino-2,2-dimethylpropionic acid (1.5 g, 5.97 mmol) in methylene chloride (13 mL) was added oxalyl chloride (0.757 g, 5.97 mmol) and dimethylformamide (30 uL). After stirring for 1 h at room temperature, the reaction mixture was cooled to 0°C and treated successively with OMe-tyrosine methyl ester hydrochloride (1.465 g, 5.97 mmol) and N-methylmorpholine (1.81 g, 17.9 mmol). Stirring for 1 h at 0-5°C was followed by distribution between CH_2Cl_2 and 0.5 N HCl. The organic phase was washed with aqueous $NaHCO_3$ and brine and dried over $MgSO_4$. Evaporation of the solvent gave a residue which was purified by chromatography. There was obtained a 61.5% yield of product as a liquid.

Example 43

Cbz-[(α , α-di-Me)-ß-Ala]-(OMe)Tyr-OH

To a 0°C solution of Cbz-[(α , α -di-Me)-ß-Ala]-(OMe)-Tyr-OMe (1.2 g, 2.71 mmol) in dioxane (15 mL) was added a solution of lithium hydroxide (0.115 g, 2.75 mmol) in water (7.5 mL). After stirring for 1 h at 0-5°C, the reaction mixture was diluted with cold water and extracted 2X with ether. The aqueous portion was acidified with 6N HCl and extracted with ether. The

Example 46 rather than Boc-Phe-OH, gave the desired product.

Example 48

3-t-Butyloxycarbonylamino-5-methylhex-1-ene

To a stirred suspension of methyltriphenyl phosphonium bromide (10.97 g, 30.70 mmol) in anhydrous tetrahydrofuran (200 mL) at -78°C (dry ice/acetone bath) under an argon atmosphere, was added n-butyl lithium (19.8 mL of a 1.55 M hexane solution) dropwise over the course of 5 min. After 10 min, the -78°C bath was replaced with a 0°C bath for .5 h, at which time the resulting orange solution was cooled again to -78°C. The solution was then added dropwise by cannula to a stirred -78°C solution of Boc-leucinal (6.00 g, 27.91 mmol) in anhydrous tetrahydrofuran (30 mL) over the course of .5 h. The mixture was then allowed to warm to room temperature during a 3 h period after which water (150 mL) was added. Extraction with hexane (4 x 100 mL) provided a combined organic phase which was washed with brine (100 mL), dried (Na_2SO_4), and concentrated to give crude 3-t-butyloxycarbonylamino-5-methylhex-1-ene (6.5 g). Chromatography with ether/hexane (1/9) provided pure 3-t-butyloxycarbonylamino-5-methylhex-1-ene (3.71 g, 60%). Mass spectrum: EI, $M^+-57 = 156$; CI, $(M + H)^+ = 214$.

Example 49

3-t-Butyloxycarbonylamino-5-methyl-1,2-oxohexane

To a stirred solution of 3-t-butyloxycarbonylamino-5-methylhex-1-ene (0.43 g, 2.0 mmol) in dichloromethane (20 mL) was added m-chloroperoxybenzoic acid (MCPBA, 1.51 g of 80% MCPBA, 7.0 mmol). After 68 h the reaction mixture was cooled to 0°C, and 0°C 10% Na_2SO_3 (5 mL) was added with stirring. After 15 min, the solid was filtered off and extracted with dichloromethane. The combined organic phase was washed sequentially with 0°C 10% Na_2SO_3 (6 mL), saturated $NaHCO_3$ (2 x 6 mL)

2-hydroxy-5-methylhexane hydrochloride (derived from 98 mg, 0.28 mmol, of 3-t-butyl-oxycarbonylamino-1-cyclohexylmercapto-2-hydroxy-5-methylhexane using the procedure of Example 51) in dry dimethylformamide (2 mL) containing N-methylmorpholine (29 mg, 0.28 mmol). Hydroxybenzotriazole (HOBT, 58 mg, 0.43 mmol) and N,N'-dicyclohexylcarbodiimide (DCC, 59 mg, 0.28 mmol) were then added sequentially. After 2 h the mixture was allowed to warm to room temperature. After 22 h the mixture was filtered, evaporated, and partitioned between ethyl acetate (18 mL) and saturated aqueous $NaHCO_3$ (6 mL). The layers were separated, and the organic phase was washed with brine (5 mL), dried (Na_2SO_4), filtered, and evaporated to a solid which was chromatographed on SiO_2 (9/1, dichloromethane/methanol) to give 86 mg (63%) of the desired compound. Mass spectrum: $(M+H)^+ = 483$.

Example 53

Boc-Phe-His Amide of 3-Amino-1-cyclohexylmercapto-2-hydroxy-5-methylhexane

The resultant compound of Example 52 was treated with methanolic HCl according to the procedure used in Example 51, yielding the corresponding deprotected HCl salt which was used as described below without further purification. To a stirred -12°C solution of Boc-Phe-OH (19.2 mg, 0.0725 mmol) in anhydrous tetrahydrofuran (3 mL) was added N-methylmorpholine (8.0 l, 0.0725 mmol) in a dropwise fashion followed by isobutylchloroformate (9.4 l, 0.0725 mmol). After 3 min, a -12°C solution of the above HCl salt in anhydrous tetrahydrofuran (2 mL) containing N-methylmorpholine (16.0 l, 0.145 mmol) was added over the course of 30 sec. After 15 min, the mixture was allowed to warm to room temperature for 3 h at which time the solvent was evaporated, and the residue was partitioned between ethyl acetate (20 mL) and saturated $NaHCO_3$

resulting solution stirred 1 h at -78°C. The reaction was quenched by adding 20 mL of saturated aqueous ammonium chloride and partitioned between water and ether. The aqueous layer was drawn off and extracted with ether. The combined organic phases were washed with 10% aqueous HCl, saturated aqueous $NaHCO_3$, and brine, dried (Na_2SO_4), filtered, and concentrated in vacuo. Recrystallization from acetone/hexanes provided the desired purified product (2.59 g, 79%). m.p. = 167-168°C. Mass spectrum: $(M+NH_4)^+$ = 393, $(M+H)^+$ = 376.

Example 56

Benzyl (2R)-2-(t-butyl acetyl)-3-phenyl-propionate

To a stirred solution of dry benzyl alcohol (0.55 mL, 5.33 mmol) in anhydrous tetrahydron furan (18 mL) under a nitrogen atomosphere at 0°C was added a hexane solution of n-butyllithium (2.58 mL; 4.00 mmol). To this solution was added the product from Example 55 in anhydrous tetrahydrofuran (10 mL). After stirring 1 h at 0°C the reaction was quenched by adding excess saturated aqueous ammonium chloride. The volatiles were removed by rotary evaporation and the resulting aqueous residue extracted two times with ether. The combined organic layers were washed with brine, dried (Na_2SO_4), filtered, and concentrated in vacuo provided an oil which was purified by chromatography on SiO_2 (15% ethyl acetate/hexanes) to provide the desired product (0.89 g, 94%) as a colorless oil. Mass spectrum: $(M)^+$ = 354.

Example 57

Benzyl (2R)-2-acetyl-3-phenylpropionate

The product from Example 56 (0.52 g, 1.47 mmol) was dissolved in a 1:1 (v:v) solution (6 mL) of trifluoroacetic acid and dichloromethane and stirred at room temperature for 1 h. The volatiles were removed in vacuo to provide the title compound (0.437 g, 100%) as

3H).

Example 60

(2R)-2-Benzyl-3-(morpholinocarbamoyl)propionate

The product from Example 58 (0.315 g, 0.86 mmol) was dissolved in ethyl acetate (5 mL) and syringed into a flask charged with 10% Pd/C (~0.3 g). The resulting suspension was exposed to 1 atm of gaseous hydrogen for 2 to 4 h. The catalyst was removed by filtration through a celite pad. The filtrate was concentrated in vacuo to provide the desired compound (0.21 g, 88%) as a cream colored foam which was employed without further purification. Mass spectrum: $(M+H)^+$ = 278.

Example 61

(2R)-2-Benzyl-3-ethoxycarbamoylpropionate

The procedure as described in Example 60 was followed employing the product from Example 59 in lieu of that from Example 58. Mass spectrum: $(M+H)^+$ = 252.

Example 62

Benzyl (2R)-2-benzyl-3-morpholinocarbonylpropionate

The product of Example 57 was converted to the title compound using the mixed anhydride method of coupling as described in Example 53. Mass spectrum: $(M)^+$ = 367.

Example 63

(2R)-2-Benzyl-3-morpholinocarbonylpropionate

The product from Example 62 was converted to the title compound following the procedure described in Example 60. Mass spectrum: $(M)^+$ = 277.

Example 64

(2R)-2-Benzyl-3-(morpholinocarbamoyl)-propionyl-His Amide of 3-Amino-1-cyclohexylmercapto-2-hydroxy-5-methylhexane

The resultant compound from Example 52 was treated with ethanolic HCl according to the procedure in Example 51, yielding the corresponding HCl salt which

Anal. calcd. for $C_{21}H_{33}NO_5S \cdot 0.5\ H_2O$: C, 59.10; H, 9.45; N, 3.28.

Found: C, 58.90; H, 9.46; N, 3.03.

Example 70

Boc-His Amide of 3-Amino-4-cyclohexyl-2-hydroxy-1-isopropylsulfonylbutane

The resultant compound of Example 69 was deprotected in analogy to Example 51 and coupled to Boc-His OH according to Example 52 to provide the desired compound. Mass spectrum: $(M)^+ = 514$.

Example 71

Boc-Leu Amide of 3-Amino-4-cyclohexyl-2-hydroxy-1-isopropylsulfonylbutane

The resultant compund of Example 69 was deprotected in analogy to Example 51 and coupled to BocLeuOH in analogy to Example 53 to provide the desired compound. Mass spectrum: $(M+H)^+ = 491$.

Example 72

(2R)-2-Benzyl-3-(morpholinocarbonyl)-propionyl-His Amide of3-Amino-4-cyclohexyl-2-hydroxy-1-isopropylsulfonylbutane

Using the procedure of Example 65 with the resultant compound of Example 70 provided the desired compound. Mass spectrum: $(M+H)^+ = 674$.

Example 73

(2R)-2-Benzyl-3-(morpholinocarbonyl)-propionyl-Leu Amide of3-Amino-4-cyclohexyl-2-hydroxy-1-isopropylsulfonylbutane

Using the procedure of Example 65 with the resultant compound of Example 71 provided the desired compound.

Example 74

(2S)-2-Benzyl-3-(ethoxycarbamoyl)-propionyl-His Amide of 3-Amino-4-cyclohexyl-2-hydroxy-1-isopropylsulfonylbutane

Using the procedure of Example 64 with the resultant compounds of Examples 61 and 70 provided the

filtered, evaporated, dissolved in ethyl acetate and extracted with 0.5 M H_3PO_4. The aqueous phase was made basic with solid K_2CO_3 and extracted with 25% isopropanol in chloroform which was dried over Na_2SO_4 and evaporated to afford 0.1520 g (65%) of the desired product as an oil. Exact mass calculated for $C_{16}H_{32}N_2O_3$: 300.2411. Found: 300.2439.

Example 78

(3S,4S)-1-(3-Methylbutylcarbonylamino)-3-hydroxy-4-t-butyloxycarbonylamino-5-cyclohexylpentane

To (3S,4S)-1-amino-3-hydroxy-4-t-butyloxy-carbonylamino-5-cyclohexylpentane (30.8 mg, 0.102 mmol) in dry methylene chloride (3 mL) at 0°C was added 4-methylpentanoyl chloride (17.0 uL, 0.123 mmol) and triethylamine (20.0 uL, 0.143 mmol). The mixture was stirred at 0°C for 1 h, evaporated, taken up in methanol (3 mL) and treated with 1 M NaOH (1 mL). After stirring for 1 h, the mixture diluted with ether, washed sequentially with 0.5 M H_3PO_4, saturated $NaHCO_3$ solution, and brine, and then dried over Na_2SO_4 and evaporated to afford 41.0 mg (100%) of the desired product as an oil.

Analysis Calculated for $C_{16}H_{28}N_2O_3$ 0.25 H_2O: C, 65.55; H, 10.63; N, 6.95.

Found: C, 65.52; H, 11.02; N, 6.77.

Example 79

Boc-Phe-His Amide of (3S,4S)-1-(3-Methylbutyl-carbonylamino)-3-hydroxy-4-amino-5-cyclohexylpentane

The resultant compound from Example 78 (36.9 mg, 0.0926 mmol) was stirred for 1 h in 4 M HCl in dioxane. The solvent was removed and dimethylformamide (0.5 mL) and N-methylmorpholine (23 uL, 0.21 mmol) were added.

To Boc-Phe-His-OH (38.5 mg, 0.0957 mmol) and 1-hydroxybenzotriazole (39.5 mg, 0.292 mmol) in dimethylformamide (0.3 mL) at -23°C was added 1-ethyl-

ester (2.50 g, 6.90 mmol) and N-methylmorpholine (2.8 mL, 25 mmol). The mixture was stirred at -10°C for 1 h and then at 25°C for 12 h. The mixture was partitioned between ethyl acetate and saturated $NaHCO_3$ solution, and extracted with ethyl acetate which was washed with water, dried over Na_2SO_4 and evaporated to afford 2.75 g (95%) of the desired product.

Analysis calculated for $C_{21}H_{28}N_4O_5$ 0.25 H_2O: C, 59.92; H, 6.82; N, 13.31.

Found: C, 59.82; H, 6.75; N, 13.13.

Example 84

Boc-Phe-dl-3-pyrazolylalanine

Boc-Phe-dl-3-pyrazolylalanine methyl ester (0.210 g, 0.505 mmol) in dioxane (1.5 mL) and water (1.0 mL) was treated with lithium hydroxide monohydrate (0.0272 g, 0.648 mmol), stirred at 25°C for 30 min and quenched with 0.32 mL 2 M HCl. The mixture was poured into chloroform, washed with water, dried over Na_2SO_4 and evaporated to afford 0.184 g (91%) of the desired compound.

Analysis calculated for $C_{20}H_{26}N_4O_5$ 0.25 H_2O: C, 59.03; H, 6.56; N, 13.77.

Found: C, 58.66; H, 6.70; N, 13.65.

Example 85

Boc-Phe-dl-3-pyrazolylalanine Amide of (3S,4S)-1-(3-Methylbutylcarbonylamino)-3-hydroxy-4-amino-5-cyclohexylpentane

Using the procedure of Example 79 with the resultant compound from Example 78 and using the resultant compound from Example 84 rather than Boc-Phe-His-OH afforded the desired compound.

Anal. Calcd for $C_{37}H_{58}N_6O_6$ 0.75 H_2O: C, 63.81; H, 8.61; N, 12.07.

Found: C, 63.95; H, 8.70; N, 11.79.

and evaporated to afford 472 mg (100%) of product as an oil.

Anal. Calcd for $C_{12}H_{19}F_2NO_3 \cdot 0.25 H_2O$: C, 53.82; H, 7.34; N, 5.23.

Found: C, 54.01; H, 7.05; N, 5.32.

Example 89

(3R,4S)-4-Cyclohexylmethyl-5-(2-mesyloxy-1,1-difluoroethyl)-2-oxazolidinone

To the resultant compound from Example 88 (460 mg, 1.75 mmol) in CH_2Cl_2 (5 mL) at 0°C was added triethylamine (0.36 mL, 2.6 mmol) and methanesulfonyl chloride (135 uL, 1.74 mmol). After stirring at 0°C for 20 min, the mixture was diluted with ethyl acetate, washed sequentially with 0.5 M H_3PO_4, saturated aqueous $NaHCO_3$ solution, and brine, then dried over Na_2SO_4 and evaporated to afford 558 mg (94%) product as an oil. Mass spectrum: FAB, $(M+H)^+ = 342$.

Example 90

(3R,4S)-4-Cyclohexylmethyl-5-(2-azido-1,1-difluoroethyl)-2-oxazolidinone

To the resultant compound from Example 89 (179.9 mg, 0.527 mmol) in dimethylformamide (DMF, 3 mL) was added NaN_3 (111.0 mg, 1.71 mmol) and the mixture was heated 100-110°C for 16 h. The mixture was poured into ethyl acetate which was washed with water and brine, dried over Na_2SO_4 and evaporated. Chromatography of the residue on silica gel with ethyl acetate/hexane mixtures afforded 116.9 mg (77%) product as an oil. Mass specrum: EI, $(M+H)^+ = 289$.

Example 91

(3R,4S)-4-Cyclohexylmethyl-5-(2-isopropylmercapto-1,1-difluoroethyl)-2-oxazolidinone

To NaH (85.0 mg, 2.22 mmol, 60% in oil, hexane washed) in DMF (4 mL) at 0°C was added isopropylmercaptan (0.40 mL, 4.3 mmol). After 15 min the

Example 95

Boc-Phe-Leu Amide of (3R,4S)-3-hydroxy-4-amino-2,2-difluoro-1-azido-5-cyclohexylpentane

To Boc-Phe-Leu-OH (169.8 mg, 0.449 mmol) in THF (2 mL) at -10°C was added N-methylmorpholine (48 uL, 0.44 mmol) followed by isobutyl chloroformate (57 uL, 0.44 mmol). After 3 min, the resultant compound from Example 93 (105.0 mg, 0.40 mmol) in THF (4 mL) was added and the reaction was stirred at -10°C 15 min then at room temperature for 2 h. The mixture was diluted with ethyl acetate, washed sequentially with 0.5 M H_3PO_4, saturated aqueous $NaHCO_3$ solution, and brine, then dried over Na_2SO_4 and evaporated. Chromatography of the residue on silica gel with ethyl acetate/hexane mixtures afforded 184.0 mg (74%) product as a glass. NMR (300 MHz, $CDCl_3$, ppm): 0.9 (d,6H), 1.4 (S,9H), 3.15-3.00 (m,2H), 3.80-3.60 (m,3H), 4.05-3.95 (m,1H), 4.4-4.2 (m,2H), 4.85 (d,1H), 5.10 (d,1H), 6.15 (d,1H).

Example 96

Boc-Phe-Leu Amide of (3R,4S)-3-hydroxy-4-amino-2,2-difluoro-1-isopropyloxy-5-cyclohexylpentane

Using the procedure of Example 95 with the resultant compound from Example 94 afforded the desired product.

Example 97

Boc-Phe-Leu Amide of (3R,4S)-3-hydroxy-4-amino-2,2-difluoro-1-isopropylmercapto-5-cyclohexylpentane

Using the procedure of Example 95 and the resultant compound from Example 91 which had been hydrolyzed to the free amine according to the procedure in Example 93 afforded the desired product.

Anal. Calcd for $C_{34}H_{55}F_2N_3O_5S$: C, 62.26; H, 8.45; N, 6.41.

Found: C, 62.32; H, 8.78; N, 6.19.

washed sequentially with cold 10% aqueous Na_2SO_3 solution, saturated aqueous $NaHCO_3$ solution and brine, then dried over Na_2SO_4 and evaporated. Chromatography on silica gel with ethyl acetate/ hexane mixtures provided 42.4 mg (81%) product as a solid.

Anal. Calcd for $C_{34}H_{55}F_2N_3O_7S$: C, 59.37; H, 8.06; N, 6.11.

Found: C, 59.05; H, 8.33; H, 5.76.

Example 101

Boc-Phe-Leu Amide of (4S)-3-oxo-4-amino-2,2-difluoro-1-azido-5-cyclohexylpentane

To oxalyl chloride (19 uL, 0.22 mmol) in CH_2Cl_2 (1 mL) at -60°C was added dimethylsulfoxide (24 uL, 0.34 mmol) in CH_2Cl_2 (1 mL). After 15 min the resultant compound from Example 95 (44.0 mg, 0.0707 mmol) in CH_2Cl_2 (3 mL) was added. The reaction was stirred for 20 min and triethylamine (75 uL, 0.54 mmol) was added. The mixture was stirred for 20 min, poured quickly into cold 20% saturated aqueous $NaHSO_4$ solution and diluted with ethyl acetate (4 mL) and hexane (12 mL). The organic phase was washed with water then brine, dried over Na_2SO_4 and evaporated. Chromatography of the residue on silica gel with ethyl acetate/hexane mixtures provided 37.3 mg (85%) product as a solid. Mass spectrum: EI, $M^+ = 620$.

Example 102

Boc-Phe-Leu Amide of (4S)-3-oxo-4-amino-2,2-difluoro-1-isopropylsulfonyl-5-cyclohexylpentane

Using the procedure of Example 101 with the resultant compound from Example 100 afforded the desired product as a solid.

Anal. Calcd for $C_{34}H_{53}F_2N_3O_7S \cdot 0.5 H_2O$: C, 58.77; H, 7.83; N, 6.05.

Found: C, 58.85; H, 7.87; N, 5.90.

Example 107

(2S,3S)-1-Amino-3-t-butyloxycarbonylamino-2-hydroxy-5-methylhexane Hydrochloride

The resultant compound of Example 106 (400 mg) dissolved in methanol containing added $CHCl_3$ was hydrogenated over 10% Pd/C (40 mg) with 3 atmospheres hydrogen. Filtration and evaporation gave the desired compound (305 mg).

Example 108

(2S,3S)-3-t-Butyloxycarbonylamino-2-hydroxy-1-(isovalerylamino)-5-methylhexane

To a solution of the resultant compound of Example 107 (1.0 mmol) and triethyl amine (2.0 mmol) in chloroform (10 mL) cooled to 0°C was added isovaleryl chloride (1.0 mmol) in $CHCl_3$ (2 mL). After 3 h, the solution was washed sequentially with 10% citric acid, saturated $NaHCO_3$, and brine. Drying and evaporating provided the desired compound.

Example 109

(2S,3S)-1-Azido-2-hydroxy-3-t-butyloxycarbonylamino-4-cyclohexylbutane

The resultant compound from Example 67 was treated according to the procedure of Example 106 to give the desired compound.

Anal. Calcd for $C_{15}H_{28}N_4O_3$: C, 57.67; H, 9.03; N, 17.93.

Found: C, 57.54; H, 9.14; N, 17.57.

Example 110

Boc-Phe-His Amide of (2S,3S)-1-(Isovalerylamino)-2-hydroxy-3-amino-5-methylhexane

Using the procedure of Example 79 with the resultant compound from Example 108 gave the desired compound.

Anal. Calcd for $C_{32}H_{50}N_6O_6 \cdot 0.5\ H_2O$: C, 61.62; H, 8.24; H, 13.47.

Found: C, 61.68; H, 8.31; N, 13.34.

(50 mL). After 3 h, the mixture was quenched (750 mL water + 100 mL brine) and extracted with ether (5 x 100 mL). The combined organic phase was washed with brine (3 x 50 mL), dried ($MgSO_4$), filtered and evaporated to an oil (2.23 g). The NMR spectrum of the crude product revealed an 82:18 mixture of 5S:5R diastereomers. Silica gel chromatography gave 80% recovery of pure diastereomers.

5S: Anal. Calcd for $C_{12}H_{19}NO_2$: C, 68.9; H, 9.1; N, 6.7. Found: C, 68.4; H, 9.2; N, 6.5. Mass spectrum: $(M+1)^+ = 210$.

5R: Mass spectrum: $(M+1)^+ = 210$.

Example 114

(3S,4S)-3-Hydroxy-4-amino-5-cyclohexyl-1-pentene

To the resultant 5S-diasteriomer from Example 113 (2.06 g, 9.84 mmol) in dioxane (180 mL) and water (120 mL) was added barium hydroxide octahydrate (6.24 g, 19.8 mmol). The mixture was refluxed for 18 h, cooled, filtered, concentrated, taken up in water and extracted with ethyl acetate which was dried over Na_2SO_4 and evaporated to afford 1.64 g (91%) of the desired product, mp: 59-61°C.

Anal. Calcd for $C_{11}H_{21}NO$: C, 72.08; H, 11.55; N, 7.64.

Found: C, 71.67; H, 11.68; N, 7.36.

Example 115

(3S,4S)-3-Hydroxy-4-tert-butoxycarbonylamino-5-cyclohexyl-1-pentene.

To the resultant compound from Example 114 (1.62 g, 8.84 mmol) in methylene chloride (20 mL) was added di-tert-butyldicarbonate (1.93 g, 8.84 mmol). The mixture was stirred for 14 h, diluted with ethyl acetate, washed sequentially with 0.5 M H_3PO_4, saturated $NaHCO_3$ solution and brine, then dried over Na_2SO_4 and evaporated to afford 2.51 g (100%) of the desired compound.

Example 120

1-Benzyloxycarbonylamino-2,3-propanediol

1-Amino-2,3-propanediol (15.2 g, 167 mmol) and NaOH (8.1 g, 204 mmol) in water (70 mL) at -10°C was treated dropwise with benzyl chloroformate (28.5 mL, 200 mmol) in ether (30 mL) over 20 min. The reaction was stirred at 0°C for 30 min then at room temperature for 2 h. The mixture was acidified with 2 M HCl and extracted with ethyl acetate which was washed with 0.5 M H_3PO_4 and brine, then dried over Na_2SO_4 and evaporated. Recrystallization of the residue from benzene afforded 16.59 g (44%) of the desired product as a white powder. NMR (300 MHz, CD_3OD, ppm): 3.12 (dd,1H), 3.28 (dd,1H), 3.50 (m,2H), 3.68 (m,1H), 5.08 (s,2H), 7.35 (m,5H).

Example 121

1-Methylamino-2,3-propanediol

Lithium aluminum hydride (7.20 g, 189 mmol) in tetrahdyrofuran (THF, 300 mL) was heated to reflux and the resultant compound from Example 120 (17.0 g, 75.5 mmol) in THF (150 mL) was added dropwise over 10 min. The mixture was relfuxed for 2 h, cooled, quenched sequentially with water (10 mL), 3 M NaOH (40 mL) and water (20 mL), then filtered and concentrated. The residue was dissolved in water which was washed with ether and evaporated. Bulb to bulb distillation of the residue afforded 2.0 g (25%) of the desired compound as an oil. NMR (300 MHz, $CDCl_3$, ppm): 2.45 (S,3H), 2.68 (dd,1H), 2.77 (dd,1H), 3.61 (dd,1H), 3.72 (dd,1H), 3.78 (M,1H).

Example 122

(N-Methyl-2,3-dihydroxypropylamino)carbonyl-(O-methyl) tyrosine methyl ester

To the resultant compound from Example 136 (1.53 g, 6.5 mmol) in dioxane (5 mL) at 0°C was added the resultant compound from Example 121 (0.684 g, 6.5

C, 60.09; H, 7.23; N, 4.67.

Found: C, 59.76; H, 7.10; N, 4.45.

Example 126

Dimethylaminocarbonyl-(O-methyl)tyrosine Methyl Ester

Prepared from dimethyl amine and the resultant compound from Example 136 according to the procedure for Example 122.

Example 127

Dimethylaminocarbonyl-(O-methyl)-tyrosine

Prepared according to the procedure of Example 123 from the resultant compound of Example 126 with the modification that the product was isolated by pouring the reaction mixture into 2 M HCl and extracting with ethyl acetate which was dried over Na_2SO_4 and evaporated. EI-MS: M^+ = 266.

Anal. Calcd for $C_{13}H_{18}N_2O_4$: C, 58.64; H, 6.81; N, 10.52.

Found: C, 58.44; H, 6.87; N, 9.95.

Example 128

3,3-Dimethylglutaric Acid Mono t-butyl Ester

3,3-Dimethylglutaric anhydride (455 mg, 3.2 mmol) in tetrahydrofuran (THF, 5 mL) was treated with sublimed potassium t-butoxide (395 mg, 3.5 mmol). After 30 min the solution was concentrated, poured into saturated $NaHCO_3$ solution and washed with ether. The aqueous phase was acidified to pH 4 with 0.5 M H_3PO_4 and extracted with chloroform which was dried over Na_2SO_4 and evaporated to afford 179 mg (26%) of the desired product as an oil. NMR (300 MHz, $CDCl_3$, ppm), 1.13 (s,6H), 1.47 (s,9H), 2.33 (s,2H), 2.45 (s,2H).

Example 129

(4-t-Butyloxycarbonyl-3,3-dimethyl)butanoyl-phenylalanine benzyl Ester

Prepared according to the procedure from Example 95 from the resultant compound from Example 128 and phenylalanine benzyl ester p-toluenesulfonic acid

Example 134

(4-t-Butyloxycarbonyl-3,3-dimethyl)butanoyl-Phe-His Amide of (3S,4S)-1-(3-Methylbutyl-carbonylamino)-3-hydroxy-4-amino-5-cyclohexylpentane

Using the procedure of Example 79 with the resultant compounds from Example 130 and Example 80 gave the desired compound.

Example 135

(4-Hydroxycarbonyl-3,3-dimethyl)butanoyl-Phe-His Amide of (3-Methylbutylcarbonylamino)-3-hydroxy-4-amino-5-cyclohexylpentane HCl Salt

The resultant compound from Example 134 was stirred in 4 M HCl/methanol for 1 h and then evaporated to provide the desired compound.

Example 136

α -Isocyanato-L-(O-methyl)tyrosine

A suspension of (O-methyl)tyrosine methyl ester hydrochloride (6 g) in toluene (125 mL) was heated at 100°C while phosgene was bubbled into the reaction mixture. After 2 h the mixture became homogeneous and the phosgene was continued for an additional 15 min. The mixture was cooled and evaporated with several benzene chasers to provide the desired product.

Example 137

2-t-Butyloxycarbonylamino-1-cyclohexyl-3-hydroxy-6-methylheptane

To a stirred -78°C solution of L-Boc-cyclohexylalaninal (1.0 g, 3.9 mmol) in anhydrous tetrahydrofuran (THF, 25 mL) was added isoamyl magnesium bromide (24.4 mL of 0.8 M solution in THF) dropwise over the course of 5 min. The mixture was warmed to 0°C for 2 h and then quenched with NH_4Cl (1.34 g, 25 mmol) in H_2O (25 mL). The THF was evaporated and the aqueous phase was extracted with ether (3 x 40 mL). The combined organic phase was washed (brine), dried (Na_2SO_4), evaporated, and chromatographed on silica

Example 140

Cbz-D-Ala-Phe-His Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane

Following the procedure of Example 138, but replacing Boc-Phe-His-OH with Cbz-D-Ala-Phe-OH and replacing the resultant compound of Example 137 with the resultant compound of Example 139 gave the desired product.

Example 141

D-Ala-Phe-His Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane

The resultant compound of Example 140 (1.0 g) in glacial acetic acid (20 mL) was hydrogenated with 10% Pd/C (450 mg) at 55 p.s.i. H_2. After 3 h, the mixture was filtered and evaporated. The residue was partitioned between ethyl acetate and saturated aqueous $NaHCO_3$ for 30 min. The organic phase was washed (brine), dried (Na_2SO_4), filtered, and evaporated to give the desired compound in 84% yield.

Example 142

D-Ser-Phe-His Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane

Following the procedures of Examples 140 and 141, but replacing Cbz-D-Ala-Phe-OH with Cbz-D-Ser-Phe-OH, gave the desired product in 39% yield.

Example 143

(OCH_3)Tyr-His Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane

Following the procedures of Examples 140 and 141, but replacing Cbz-D-Ala-Phe-OH with Cbz-(OCH_3)-Tyr, gave the desired product.

Example 144

(Imidazol-4-yl)acetyl-(OCH_3)Tyr-His Amide of 2-Amino-1-cyclohexyl-3-hydroxy-6-methylheptane

Following the procedure of Example 138, but replacing Boc-Phe-His-OH with (imidazol-4-yl)acetic

mixtures to give 378 mg, 67% of the desired material. Mass spectrum: M_s^+ = 434.

Example 148

Boc-Phe-Ala Amide of 4-Amino-3-hydroxy-6-methyl-1-(4-methylvaleryl)amino-1-phenylheptane.

Following the deprotection procedure of Example 138 and using the resultant compound of Example 147 gave the corresponding hydrochloride which was coupled to Boc-Phe-Ala according to the procedures of Example 16. The desired compound was obtained in 98% yield.

Mass spectrum: $(M+H)^+$ = 653.

Anal. calcd.: C, 68.1; H, 8.7; N, 8.6. Found: C, 68.1; H, 9.0; 8.3.

Example 149

4-t-Butyloxycarbonylamino-1-cyclohexyl-3-hydroxy-6-methyl-1-(4-methylvaleryl)aminoheptane

The resultant compound of Example 147 (70.0 mg, 0.161 mmol) in glacial acetic acid (15 ml) was hydrogenated over Pt black (70 mg) for 22 h. The mixture was filtered, diluted with H_2O (50 ml) and brine (50 ml), and extracted with ether (50 ml). The organic phase was washed with water (2 x 50 ml), saturated K_2CO_3 (25 ml), and brine (10 ml). Drying ($MgSO_4$) and evaporating gave 54 mg of the desired material. Mass spectrum: $(M+H)^+$ = 441.

Anal. calcd.: C, 68.1; H, 11.0; N, 6.4.

Found: C, 68.3; H, 11.5; N, 6.3.

Example 150

Boc-Phe-Ala-amide of 4-Amino-1-cyclohexyl-3-hydroxy-6-methyl-1-(4-methylvaleryl)aminoheptane

Following the deprotection procedure of Example 138 and using the resultant compound of Example 149 gave the corresponding amine hydrochloride which was coupled to Boc-Phe-Ala according to the procedure of Example 16, the desired compound was obtained in 89%

Example 155

4-t-Butyloxycarbonylamino-3-hydroxy-6-methylheptanoic Acid Ethyl Ester

To diisopropylamine (7.7 g, 0.077 mol) in dry tetrahydrofuran (20 ml) cooled to -20°C under an argon atmosphere was added dropwise n-butllithium in hexane (1.46 M, 52.4 ml, 0.077 mol). The solution was stirred 15 min, the temperature lowered to -78°C and dry ethyl acetate (6.7 g, 0.077 mol) added dropwise while maintaining the temperature below -75°C. The solution was stirred 10 min and a precooled (-78°C) tetrahydrofuran solution of Boc-L-leucinal (11 g, 0.051 mol) was added. After 30 min, 2 M HCl (40 ml) was added and the mixture was slowly warmed to 10°C and extracted with ether (3 x 200 ml). The combined ethereal extract was washed with satd. sodium chloride (NaCl) and dried with magnesium sulfate ($MgSO_4$) and filtered. Evaporation of the filtrate in vacuo gave 14 g of crude product which was purified by flash column chromatography (20% ethylacetate in hexane). Obtained 6 g of Boc-Sta-OEt.

H' NMR (300 MHz, $CDCl_3$, ppm), 0.93 (d,6H), 1.27 (t,3H), 1.3-1.75 (m,3H), 1.44 (S,9H), 2.50 (m,2H), 3.35 (s,1H), 3.63 (br m,1H), 4.03 (br m,1H), 4.18 (q,2H), 4.75 (br d,1H).

Example 156

4-t-Butyloxycarbonylamino-3-hydroxy-6-methylheptanoic Acid (Boc-Statine)

To 0.8 g of Boc-Sta-OEt in 24 ml of dioxane/water (2:1) was added 120 mg of lithium hydroxide at 0°C. After 10 min, the mixture was warmed to room temperature. After 1 h, the mixture was poured to a 10% solution of potassium bisulfate and extracted with ethyl acetate (3 x 100 ml). The combined organic phase was washed with a satd. NaCl solution and dried with $MgSO_4$ and filtered. Evaporation of the filtrate

Example 160

Boc-Sta Amide of 2-Methylbutylamine

Using the procedure of Example 157, but replacing benzylamine with 2-methylbutylamine gave the desired compound (86% yield). Mass spectrum: M^+ = 344.

Example 161

Boc-Sta Amide of Isoleucinol

Using the procedure of Example 157, but replacing benzylamine with isoleucinol gave the desired compound (85% yield). Mass spectrum: M^+ = 374.

Example 162

Boc-Sta Amide of Methioninol

Using the procedure of Example 157, but replacing benzylamine with methioninol gave the desired compound (83% yield). Mass spectrum: M^+ = 392.

Example 163

Amine Hydrochloride of Boc-Sta Amide of Benzyl Amine

Boc-Sta amide of benzylamine (100 mg, 0.27 mmol) was dissolved in 3 ml of 4N HCl and stirred for 10 min. The solvent was evaporated in vacuo and the crude product, the amine hydrochloride from deprotection of the N-terminal of Boc-Sta-amide of benzylamine was dried under high vacuum for 12 h at room temperature. Likewise, the amine hydrochloride of the compounds in Example 158 to Example 161 are prepared by the same procedure.

Example 164

Boc-Phe-His-Sta Amide of Benzylamine

To the amine hydrochloride of Boc-Sta amide of benzylamine (200 mg, 0.34 mmol) in 4 ml of dimethyl formamide (DMF) was added triethylamine (47 uL, 0.34 mmol). The solution was cooled to 0°C and Boc-Phe-His-OH was added (136 mg, 0.34 mmol), followed by 1-hydroxybenzotriazole (70 mg, 0.51 mmol) and then dicyclohexylcarbodiimide (72 mg, 0.34 mmol). The

Example 166

Boc-Phe-His-Sta Amide of Isobutylamine

Using the procedure of Example 164, but using the amine hydrochloride of Boc-Sta amide of isobutylamine gave the desired compound (60% yield). m.p. 163-164°C. Mass spectrum: $(M+H)^+ = 615$.

Example 167

Boc-(α-Naphthyl)Ala-Ala-Sta Amide of Isoleucinol

Using the procedure of Example 165, but using the amine hydrochloride of Boc-Sta amide of isoleucinol gave the desired compound (81% yield). m.p. 181-182°C. Mass spectrum: $(M+H)^+ = 643$.

Example 168

Boc-(α-Naphthyl)Ala-Ala-Sta Amide of Methioninol

Using the procedure of Example 165, but using the amine hydrochloride of the Boc-Sta amide of methioninol gave the desired product (76% yield). m.p. 183-184°C. Mass spectrum: $(M+H)^+ = 661$.

Example 169

Boc-His-Sta Amide of 2-Methylbutylamine

Using the procedure of Example 164, but using the amine hydrochloride of Boc-Sta amide of 2-methylbutylamine and replacing Boc-Phe-His with Boc-His-OH gave the desired compound (60% yield). m.p. 115-116°C. Mass spectrum: $M^+ = 681$.

Example 170

t-Butylacetyl-Phe-His-Sta Amide of 2-Methylbutylamine

Using the procedure of 165, but using the amine hydrochloride of Example 169 and replacing Boc(-Naphthyl)-Ala-Ala-OH with t-butylacetyl-Phe-OH gave the desired compound (45% yield). m.p. 186-188°C. Mass spectrum: $(M+H)^+ = 627$.

Example 171

Boc-p-iodo-Phe-His-Sta Amide of 2-Methylbutylamine

Using the procedure of Example 165, but using the amine hydrochloride of Example 169 and replacing

M^+ = 343.

Example 177

4-t-Butyloxycarbonylamino-3-hydroxy-5-cyclohexylpentanoic Acid (Boc-ACHPA)

Using the procedure of Example 156, but using the compound from Example 176, gave the desired compound (100% yield). Mass spectrum: M^+ = 315.

Example 178

Boc-ACHPA Amide of Isopentylamine

Using the procedure of Example 157, but replacing Boc-Sta with Boc-ACHPA and benzyl amine with isopentylamine gave the desired compound (70% yield). Mass spectrum: M^+ = 384.

Example 179

Boc-Phe-His-ACHPA Amide of Isopentylamine

Using the procedure of Example 164, but using the amine hydrochloride of Boc-ACHPA amide of isopentylamine gave the desired compound (42% yield). m.p. 108-110°C. Mass spectrum: (M + H) = 669.

Example 180

4-t-Butyloxycarbonylamino-2-benzyloxy-3-hydroxy-5-cyclohexylpentanoic Acid Methyl Ester

Using the procedure of Example 155, but replacing Boc-leucinal with Boc-cyclohexylalaninal, and replacing ethyl acetate with benzyloxymethyl acetate gave the desired compound in 14.5% yield. Mass spectrum: M^+ = 435.

Example 181

4-t-Butyloxycarbonylamino-2-benzyloxy-3-hydroxy-5-cyclohexylpentanoic Acid

Using the procedure of Example 156, but using the compound from Example 180 gave the desired compound (100% yield). Mass spectrum: M^+ = 431.

replacing Boc-(α-Naphthyl)-Ala-Ala-OH with Boc-Phe-Ala-OH and using the amine hydrochloride in Example 184 gave the desired product (59% yield). Mass spectrum: $(M+H)^+$ = 709.

Example 187

Boc-Phe-Histidinyl-4-amino-2-benzyloxy-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 166, but using the amine hydrochloride in Example 184 gave the desired product (40% yield). Mass spectrum: $(M+H)^+$ = 776.

Example 188

Boc-Phe-Alaninyl-4-amino-2,3-dihydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 165, but replacing Boc-(α -Naphthyl)-Ala-Ala-OH with Boc-Phe-Ala-OH and using the amine hydrochloride in Example 185 gave the desired product. Mass spectrum: $(M+H)^+$ = 619.

Example 189

Boc-Phe-Histidinyl-4-amino-2,3-dihydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure in Example 165, but using the amine hydrochloride in Example 185 gave the desired product (35% yield). Mass spectrum: $(M+H)^+$ = 685.

Example 190

4-t-Butyloxycarbonylamino-2-methoxy-3-hydroxy-5-cyclohexylpentanoic Acid Ethyl Ester

Using the procedure of Example 155 but replacing Boc-Leucinal with Boc-cyclohexylalaninal, and replacing ethyl acetate with methoxy ethyl acetate gave the desired product (33% yield). Mass spectrum: M^+ = 407.

Example 191

4-t-Butyloxycarbonylamino-2-methoxy-3-hydroxy-5-cyclohexylpentanoic Acid

Using the procedure of Example 156, but using

(100% yield). Mass spectrum: $M^+ = 355$.

Example 197

4-Boc-amino-2-allyl-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 164, but replacing Boc-Phe-His-OH with the compound in Example 196 and using 2-methylbutylamine instead of an amine hydrochloride gave the desired product (50% yield). Mass spectrum: $M^+ = 424$.

Example 198

Amine Hydrochloride of 4-t-Boc-amino-2-allyl-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 167, but replacing Boc-Sta amide of benzylamine with the compound in Example 59 gave the desired compound (100% yield).

Example 199

Boc-Phe-Histidinyl-4-amino-2-allyl-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

Using the procedure of Example 164, but using the amine hydrochloride in Example 199 gave the desired product (40% yield). Mass spectrum: $(M+H)^+ = 709$.

Example 200

Boc-Phe-Histidinyl-4-amino-2-propyl-3-hydroxy-5-cyclohexylpentanoic Acid Amide of 2-Methylbutylamine

A solution of 11 mg of the compound of Example 199 in methanol with 3 mg of 10% palladium on charcoal added was stirred vigorously under hydrogen atmosphere for 2 h at room temperature. The catalyst was filtered off and the filtrate concentrated to give a colorless oil. Purification by silica gel column chromatography gave 11 mg of pure product (100% yield). Mass spectrum: $(M+H)^+ = 711$.

equivalents of BH_3:THF (1 M). The solution was stirred at 0°C for 30 min and then at room temperature for 3.5 h. The reaction was carefully quenched with cold water. The product was extracted with ethyl acetate (3 x 300 ml) and the combined organic phase washed with brine and dried with anhydrous $MgSO_4$. Filtration and concentration gave an oil which was purified by silica gel column chromatography (10% MeOH/CH_2Cl_2) to give 7.1 g of white solid. Mass spectrum: M^+ = 239.

Example 206

4-Hydroxyethyl-oxazolidin-2-one

To 1.1 g of the compound in Example 204 in 25 ml of DMF at 0°C was added 360 mg of sodium hydride (60% oil dispersion) portionwise. At the end of the addition, the suspension was stirred at 0°C for 2 h and then at room temperature overnight. The solvent was evaporated under reduced pressure. The crude oily product was purified by silica gel column chromatography (10% MeOH/CH_2Cl_2) to give 580 mg of white solid. m.p. 90-91°C. Mass spectrum: M^+ = 131.

Example 207

(Oxazolidin-2-one-4-yl)ethanal

To 520 mg of the product from Example 206 in 110 ml of CH_2Cl_2 was added 2.1 g of pyridinium dichromate. The suspension was stirred at room temperature overnight. The reaction mixture was filtered through a thightly packed layer of celite and concentrated under reduced pressure. The crude brown oil was purified by silica gel column chromatography (5% MeOH/CH_2Cl_2) to give 270 mg of pure aldehyde. Mass spectrum: M^+ = 129.

Example 208

4-[(1,3-Dithiolan-2-yl)methyl]oxazolidin-2-one

To a solution of 370 mg of the aldehyde from Example 207 in 30 ml of dichloromethane was added

ethanol/water (25 ml/25 ml) was added 785 mg of barium hydroxide (2 equivalents). The suspension was heated to reflux for 16 h. Upon cooling to room temperature, the solid formed was filtered and washed with methanol. The solution was concentrated under reduced pressure. The residue was dissolved in 20 ml of dichloromethane. To this solution was added 1.5 equivalents of di-t-butyldicarbonate. After 2 h, the solvent was removed under reduced pressure and the crude product was purified by silica gel column chromatography (CH_2Cl_2/EtOAc 6.4) to give 430 mg of pure product. Mass spectrum: $M^+ = 279$.

Example 213

2-t-Butyloxycarbonylamino-
3-(1',3'-dithian-2'-yl)-propanol

Using 110 mg of the product from Example 209 and the procedure in Example 212 gave 90 mg of the desired product.

Example 214

2-Benzyloxycarbonylamino-
3-(1',3'-dioxolan-2'-yl)-propanol

To 200 mg of the oxazolidinone from Example HS-56 in dioxane/ water (15 ml/15 ml) was added 400 mg of barium hydroxide (2 equivalents). The suspension was heated to reflux for 3.5 h, at which time all the starting material was consumed. The suspension was cooled to room temperature and filtered. The solid was washed with methanol and the solution was concentrated under reduced pressure. The residue was dissolved in 10 ml of dichloromethane and 1.5 equivalents of N-(benzyloxycarbonyloxy)-succinimide was added. After 1 h, the solution was concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (5% MeOH/CH_2Cl_2) to give 305 mg of the desired product. Mass spectrum: $M^+ = 281$, m.p. 85-86°C.

which was purified by silica gel column chromatography (20% EtOAc/80% CH_2Cl_2) to give 258 mg of the desired product. Mass spectrum: $M^+ = 365$.

Example 217

3-Hydroxy-4-t-butyloxycarbonylamino-5-(1',3'-dithian-2'-yl)-pentanoic Acid Ethyl Ester

Using the same sequence of reactions outlined in Example 216 and using 140 mg of the product from Example 213 as the starting material provided 57 mg of the desired product after silica gel column chromatography. (CH_2Cl_2/EtOAc 2:8). Mass spectrum: $M^+ = 379$.

Example 218

3-Hydroxy-4-benzyloxycarbonylamino-5-(1',3'-dioxolan-2'-yl)-pentanoic Acid Ethyl Ester

Using the same sequence of reactions outlined in Example 216 and using 270 mg of the product from Example 214 as the starting material gave 210 mg of the desired product after silica gel column chromatography (CH_2Cl_2/EtOAc 1:1). Mass spectrum: $M^+ = 333$.

Example 219

3-Hydroxy-4-benzyloxycarbonylamino-5-(1',3'-dioxan-2'-yl)-pentanoic Acid Ethyl Ester

Using the same sequence of reactions outlined in Example 216 and using 274 mg of the product from Example 215 as starting material gave 200 mg of the desired product after silica gel column chromatography (CH_2Cl_2/EtOAc 6:4). Mass spectrum: $M^+ = 347$.

Example 220

3-Hydroxy-4-t-butyloxycarbonylamino-5-(1',3'-dithiolan-2'-yl)-pentanoic Acid

To a solution of 250 mg of the product from Example 216 in 6 ml of dioxane/water (1:1) was added 1.2 equivalents of lithium hydroxide. The solution was stirred at room temperature for 30 min. The solution was acidified with 10% potassium hydrogen sulfate

10% potassium hydrogen sulfate solution and extracted with ethyl acetate (3 x 50 ml), dried with anhydrous $MgSO_4$ and filtered. The solution was concentrated under reduced pressure to give a pale yellow oil which was purified by silica gel column chromatography (2% $MeOH/CH_2Cl_2$) to give 200 mg of pure product. Mass spectrum: $M^+ = 406$.

Example 225

3-Hydroxy-4-t-butyloxycarbonylamino-5-(1',3'-dithian-2'-yl)-pentanoic Acid Amide of 2-methylbutylamine

Using the procedure described in Example 224 and using 50 mg of the product from Example 221 as the starting material gave 49 mg of the desired product after silica gel column chromatography (3% MeOH/CH_2Cl_2). Mass spectrum: $M^+ = 420$.

Example 226

3-Hydroxy-4-benzyloxycarbonylamino-5-(1',3'-dioxolan-2'-yl)-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure described in Example 224 and using 147 mg of the product from Example 222 as the starting material gave 124 mg of the desired product after silica gel column chromatography (2% MeOH/CH_2Cl_2). Mass spectrum: $M^+ = 408$.

Example 227

3-Hydroxy-4-benzyloxycarbonylamino-5-(1',3'-dioxan-2'-yl)-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure described in Example 224 and using 200 mg of the product from Example 223 as the starting material gave 190 mg of the desired product after silica gel column chromatography (2% MeOH/CH_2Cl_2). Mass spectrum: $M^+ = 422$.

material gave the desired product which was used without further purification.

Example 232

Boc-Phe-S-methylcysteinyl-[3-hydroxy-4-amino-5-(1',3'-dithiolan-2'-yl)]-pentanoic Acid Amide of 2-Methylbutylamine

To a solution of 57 mg of Boc-Phe-S-methyl-cysteine in 5 ml of THF at -15°C was added 0.017 ml of N-methylmorpholine, followed by 0.020 ml of isobutyl-chloroformate. After 10 min, a solution of the product from Example 228 (starting with 49 mg) in 5 ml of THF with 0.016 ml of N-methylmorpholine was added. After the solution was stirred at -15°C for 1 h, it was poured into 10% potassium hydrogen sulfate and extracted with ethyl acetate (3 x 50 ml), dried with anhydrous $MgSO_4$ and filtered. The solvent was evaporated under reduced pressure. The crude product obtained was purified by silica gel column chromatography (CH_2Cl_2/EtOAc 3:7) to give 36 mg of product. Mass spectrum: $(M + H)^+$ = 671; m.p. = 144-145°C.

Example 233

Boc-Phe-S-methylcysteinyl-[3-hydroxy-4-amino-5-(1',3'-dithian-2'-yl)]-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure described in Example 232 and using 57 mg of Boc-Phe-S-methyl-cysteine and the product from Example 229 (from 44 mg of starting material) gave 25 mg of the desired product after silica gel column chromatography (CH_2Cl_2/EtOAc 3:7). Mass spectrum: $(M+H)^+$ = 685.

Example 234

Boc-Phe-S-methylcysteinyl-[3-hydroxy-4-amino-5-(1',3'-dioxolan-2'-yl)]-pentanoic Acid Amide of 2-Methylbutylamine

Using the procedure described in Example 232 and using 63 mg of Boc-Phe-S-methylcysteine, 40 mg of

concentrated under reduced pressure and the crude product was purified by silica gel column chromatography (5% MeOH/CH_2Cl_2)' to give 12 mg of product. Mass spectrum: $(M+H)^+$ = 691.

Example 238

2(R,S)-(4-morpholinylcarbonylmethyl)-3-(1'-naphthyl)-propionic Acid

To 50 ml of absolute ethanol was added 2 g of sodium metal. The suspension was stirred vigorously until all the sodium dissolved and the evolution of hydrogen ceased. To this solution of sodium ethoxide was added a solution of 11.6 g of diethylsuccinate in 10.4 g of 1-naphthaldehyde. The solution was heated to reflux for 3 h, at which time it was cooled to room temperature and concentrated on the rotavap. The residue was dissolved in 320 ml of water and extracted 6 times with 100 ml portions of ether. The aqueous layer was acidified with 2N HCl and extracted with 2 x 300 ml of ether and dried with anhydrous magnesium sulfate. Evaporation of the solvent gave a yellow gummy solid which was hydrogenated to the saturated acid using Pd/C as catalyst. Coupling of the resulting saturated acid to morpholine using the mixed anhydride method described in Example 17 followed by ester hydrolysis using the procedure of Example 156 gave the desired acid. Mass spectrum: $(M+H)^+$ = 328.

Example 239

Boc-ACHPA-amide of 2-methylbutylamine

Using the procedure of Example 157, but replacing Boc-Sta with Boc-ACHPA and benzylamine with 2-methylbutylamine gave the desired compound (76% yield). Mass spectrum: M^+ = 384.

Example 240

Boc-His-ACHPA-amide of 2-methylbutylamine

Using the procedure of Example 164, but using the amine hydrochloride of Boc-ACHPA-amide of

was then dissolved in ~100 ml of methylene chloride and 1.1 equivalent of 3-pyrroline (75% pure) was added dropwise at 0°C. After 15 min, the reaction mixture was washed with 0.5 N HCl and methylene chloride. The organic layer was washed with aqueous $NaHCO_3$ and dried over $MgSO_4$. Evaporation of the solvent gave 3-pyrrolinylcarbonyl-Phe-methyl ester which was cis-hydroxylated under the following conditions: 2.5 g of the 3-pyrrolinylcarbonyl-Phe-methyl ester was dissolved in 50 ml of THF and 1 ml of a 2.5% solution of OsO_4 in t-butanol was added, followed by 1.15 g of N-methylmorpholine-N-oxide. After 1 h, the solvent was evaporated and the residue dissolved in 150 ml of ethyl acetate and washed with dilute Na_2SO_3 solution, satd. $NaHCO_3$ solution and then dried with $MgSO_4$. Evaporation of the solvent gave a gummy solid which was purified by SiO_2 column chromatography (5% MeOH/CH_2Cl_2) to give the desired compound (65% yield). Mass spectrum: $M^+ = 308$.

Example 245

(3,4-cis-dihydroxypyrrolidinylcarbonyl)-Phe-OH

Using the procedure of Example 156 and replacing Boc-Sta-OEt with the compound from Example 244 gave the desired compound. Mass spectrum: $M^+ = 294$.

Example 246

(3,4-cis-dihydroxypyrrolidinylcarbonyl)-O-methyl-Tyr-methyl Ester

Using the procedure described in Example 244 and replacing L-phenylalanine methyl ester with L-O-methyl-tyrosine methyl ester gave the desired compound. Mass spectrum: $M^+ = 338$.

Example 247

(3,4-cis-dihydroxypyrrolidinylcarbonyl)-O-methyl-Tyr-OH

Using the procedure described in Example 156 and replacing Boc-Sta-OEt with the compound from

hydrochloride (6 g) in toluene (125 ml) was heated to 100°C and phosgene gas was bubbled into the reaction mixture. After approximately 1.5 h, the mixture became homogeneous. The bubbling of phosgene was continued for 10 more min. The solvent was then evaporated and the residue chased with benzene several times. The residue was then dissolved in ~100 ml of methylene chloride and cooled to ~0°C, and 1.1 equivalent of thiomorpholine was added dropwise. After 10 min the solution was washed with 1N HCl and the organic layer was dried with $MgSO_4$. Evaporation of solvent gave 5.5 g of product. Mass spectrum: $M^+ = 308$.

Example 253

[(4-Sulphonylmorpholinyl)carbonyl]-Phe Methyl Ester

To 2 g of the product from Example 252 in 100 ml of methylene chloride was added 2.94 g of a meta-chloroperbenzoic acid at 0°C. After 30 min the solvent was evaporated and ether solution was washed with 10% sodium sulfite solution and then with satd. sodium bicarbonate several times. The organic layer was dried with $MgSO_4$ and evaporation of the solvent gave a white solid which was purified by silica gel column chromatography (20% EtOAc/80%/CH_2Cl_2) to give 2.10 g (95%) of pure product. Mass spectrum: $M^+ = 340$.

Example 254

[(4-sulfonylmorpholinyl)carbonyl]-Phe-OH

Using the procedure described in Example 156, but replacing Boc-Sta-OEt with the compound from Example 253 gave the desired compound.

Example 255

[(4-sulfonylmorpholinyl)carbonyl]-Phe-O-methyl-Ser-ACHPA-amide of2-Methylbutylamine

Using the procedure described in Example 165, but replacing Boc-(α-Naphthyl)Ala-Ala-OH with the product from Example 254 and using the amine hydrochloride of the compound from Example 250 gave the

by flash column chromatography using 3:1 chloroform/ethyl acetate. Mass spectrum: M^+ = 396.

Example 258

N-Methyl-4-hydroxy-5-t-butyloxycarbonylamino-6-cyclohexylhex-1-ene-2-carboxamide

Using the procedure of Example 256, but replacing N-(3-methylbutyl)-2-methyl-propenamide with N,2-dimethylpropenamide gave a ca. 1:1 mixture of (4S,5S) product (R_f .13) and (4R,5S) product (R_f .08, 3:2 chloroform/ethyl acetate) in 61% yield which were partially separated by flash column chromatography using 3:2 chloroform/ethyl acetate. Mass spectrum: M^+ = 354.

Example 259

N-(2,2-Dimethyl-3-(N,N-dimethylamino)propyl)-4-hydroxy-5-t-butyloxycarbonylamino-6-cyclohexylhex-1-ene-2-carboxamide

Using the procedure of Example 256, but replacing N-(3-methylbutyl)-2-methylpropenamide with N-(2,2-dimethyl-3-(N,N-dimethylamino)propyl)-2-methyl-propenamide gave a ca. 1:1 mixture of (4S,5S) and (4R,5S) products (R_f .39, 1:1 methanol/chloroform) in 77% yield which were separated from remaining starting material by preparative thin layer chromatography using 1:1 methanol/chloroform. Further separation of diastereomers was not feasible. Mass spectrum: M^+ = 453.

Example 260

N-(3-t-Butyloxycarbonylamino-2,2-dimethylpropyl)-4-hydroxy-6-cyclohexyl-5-triphenyl-methylaminohex-1-ene-2-carboxamide

A solution of N-t-butyloxycarbonyl-N'-2-methyl-propenoyl-2,2-dimethyl-1,3-propanediamine (270 mg, 1.0 mmol) in 10 ml of dry tetrahydrofuran was cooled under a N_2 atmosphere to -78°C, treated dropwise with 1.68 ml (3.0 mmol) of n-butyllithium in hexane, stirred at -78°C

after flash column chromatography using 5:1 chloroform/ethyl acetate, the desired (2R) (R_f .44) and (2S) (R_f .37, 3:2 chloroform/ethyl acetate) diastereomeric products in 53% and 47% yields, respectively. For each isomer, mass spectrum: M^+ = 412.

Example 263

(4S,5S)-N-(3-Methylbutyl)-5-t-butyloxycarbonylamino-6-cyclohexylhexane-1,4-diol-2-carboxamide

Ammonia (ca. 10 ml) was condensed into a flask containing 10 ml of dry tetrahydrofuran precooled to -78°C. The resulting mixture was treated with ca. 30 mg of lithium metal, stirred at -78°C for 10 min, treated with a solution of the mixture of epoxides produced in Example 261 in 1 ml of tetrahydrofuran, stirred at -78°C for 6 min and cautiously poured into a rapidly stirred mixture of ether and saturated aqueous NH_4Cl. The organic layer was separated, dried over $MgSO_4$ and reduced in vacuo. Separation by flash column chromatography using 1.8:1 chloroform/ethyl acetate followed by 13:1 chloroform/methanol gave a 66% yield (78% based on recovered starting material) of the desired compound as an inseparable 1.5:1 mixture of diastereomers (R_f .04, 3:2 chloroform/ethyl acetate). Mass spectrum: $(M+1)^+$ = 429.

Example 264

(4S,5S)-N-(3-Methylbutyl)-1-acetoxy-4-hydroxy-5-t-butyloxycarbonylamino-6-cyclohexylhexane-2-carboxamide

A solution of the resultant compound of Example 263 (40.2 mg, 0.094 mmol) in 0.3 ml of dry dichloromethane was treated sequentially with 14.5 uL (0.10 mmol) of triethylamine and 9.8 uL (0.10 mmol) of acetyl chloride. After being allowed to stir overnight, the mixture was partitioned between dichloromethane and water, dried over Na_2SO_4 and purified by flash

was treated sequentially with 170 ml (0.017 mmol) of osmium tetroxide in t-butanol and ca. 100 mg (0.7 mmol) of 4-methylmorpholine-N-oxide. After stirring for 24 h, the solution was diluted with 50 ml of ether, washed sequentially with five 4 ml portions of 10% $Na_2S_2O_3$, 4 ml of 1M HCl, 4 ml of H_2O and 4 ml of saturated aqueous $NaHCO_3$ and dried over $MgSO_4$. Separation by flash column chromatography using 19:1 chloroform/methanol gave an 88% yield of the desired compound as a 1:1 mixture of diastereomers (R_f .35, 12:1 chloroform/methanol). Mass spectrum: $M^+ = 444$.

Example 268

(4S,5S)-N-Isobutyl-5-t-butyloxycarbonylamino-6-cyclohexylhex-1-ene-3,4-diol-2-carboxamide

A solution of 173 mg (0.44 mmol) of the (4S,5S) diastereomer from Example 257 and 68 mg (0.52 mmol) of selenious acid in 4 ml of dioxane was heated at 70°C for 16 h and 95°C for 4 h. After cooling, filtration through Celite and separation by flash column chromatography using 7:3 chloroform/ethyl acetate gave a 50% yield of the desired compound (R_f .25, 7:3 chloroform/ethyl acetate) as a 1:1 mixture of diastereomers. Mass spectrum: $M^+ = 412$.

Example 269

(4S,5S)-N-(3-Methylbutyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide hydrochloride

The (4S,5S) diastereomer from Example 256 (31.5 mg, 0.077 mmol) was treated with 0.5 ml of a 4 M solution of HCl in dioxane and allowed to stand at ambient temperature for 1 h. After removal of the solvent in vacuo, the residue was treated twice with 0.5 ml of anhydrous ether followed each time by removal of the solvent in vacuo. The crude amine hydrochloride was used without further purification.

oil was digested twice with hexane, followed each time by decantation. Removal of the last traces of solvent gave the desired compound as a mixture of diastereomers which was used without further purification.

Example 274

(4S,5S)-N-(3-Methylbutyl)-1-acetoxy-5-amino-4-hydroxy-6-cyclohexylhexane-2-carboxamide hydrochloride

Using the procedure of Example 269 with the resultant compound of Example 264 gave the desired compound.

Example 275

(2R,4S,5S)-N-Isobutyl-5-amino-1-azido-6-cyclohexylhexan-2,4-diol-2-carboxamide hydrochloride

Using the procedure of Example 269 with the resultant compound of Example 265 gave the desired compound.

Example 276

(2S,3S,5S)-N-Isobutyl-2-amino-1-cyclohexyl-7-methyloctan-3,5-diol-5-carboxamide hydrochloride

Using the procedure of Example 269 with the resultant compound of Example 266 gave the desired compound.

Example 277

(2S,4S,5S)-N-Isobutyl-4-amino-1-chloro-6-cyclohexylhexane-2,4-diol-2-carboxamide hydrochloride

Using the procedure of Example 269 with the resultant (2R) diastereomer of Example 262 gave the desired compound.

Example 278

(4S,5S)-N-(3-Methylbutyl)-5-amino-6-cyclohexylhexane-1,2,4-triol-2-carboxamide hydrochloride

Using the procedure of Example 269 with the resultant compound of Example 267 gave the desired compound as a mixture of diastereomers.

overnight. The resulting solution was treated with 0.5 ml of 10% $Na_2S_2O_3$, allowed to stir for 1 h, diluted with 3 ml of ethyl acetate, extracted with aqueous $NaHCO_3$, dried over $MgSO_4$ and concentrated in vacuo. Purification by flash column chromatography using 1-2% methanol in chloroform gave 7.6 mg (67%) of the desired compound as a ca. 1:1 mixture of diastereomers (R_f .38, .41, 7.5% methanol in chloroform). Mass spectrum: $(M+H)^+$ = 645.

Example 282

Boc-Phe-His amide of (4S,5S)-N-(3-methylbutyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide

A solution of 52 mg (0.13 mmol) of Boc-Phe-His-OH and 52 mg (0.39 mmol) of 1-hydroxybenzotriazole monohydrate in 0.6 ml of dimethylformamide was cooled to -23°C, treated with 25 mg (0.13 mmol) of 1-ethyl-3-(dimethylaminopropyl)carbodiimide hydrochloride, and allowed to stir for 1 h. A solution of 0.13 mmol of the resultant compound of Example 269 and 29 uL (0.26 mmol) of 4-methylmorpholine in 0.6 ml of dimethylformamide was subsequently added, and the resulting solution was stirred at -23°C for 3 h and at ambient temperature for 16 h. After dilution with 10 ml of ethyl acetate, the solution was washed sequentially with 1 ml of saturated aqueous $NaHCO_3$ and 1 ml of H_2O, dried over $MgSO_4$, and concentrated in vacuo. Purification by flash column chromatography using 10% methanol in chloroform gave 49 mg (55%) of the desired compound (R_f .20, 10% methanol in chloroform) which was recrystallized from tetrahydrofuran/hexane, m.p. 178-180°C (dec). Mass spectrum: M^+ = 694.

Example 283

Boc-Phe-His amide of N-(2,2-dimethyl-3-(N,N-dimethylamino)propyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide

A solution of 3.09 g (6.83 mmol) of the

chromatography using 15% methanol in chloroform gave the desired compound as a mixture of diastereomers. Mass spectrum: $(M+H)^+$ = 713.

Example 286

Boc-Phe-His Amide of (2R,4S,5S)-N-isobutyl-5-amino-1-azido-6-cyclohexylhexane-2,4-diol-2-carboxamide

Using the procedure of Example 283 with the resultant compound of Example 275 gave, after purification by flash column chromatography using 5% methanol in chloroform, a 72% yield of the desired compound (R_f .23, 7.5% methanol in chloroform). Mass spectrum: $(M+H)^+$ = 740..

Example 287

(5N)-Boc-Phe-His amide of (2R,3S,5S)-N-isobutyl-6-cyclohexyl-1,5-diaminohexane-2,4-diol-2-carboxamide

A solution of 8.2 mg (0.011 mmol) of the resultant compound of Example 286, 2 uL (0.035 mmol) of glacial acetic acid, and ca. 5 mg of 10% palladium on carbon in 0.5 ml of methanol was stirred overnight under a H_2 atmosphere. After dilution with chloroform, the mixture was filtered through Celite, concentrated in vacuo, filtered through a plug of basic alumina using 1:1 methanol/ethyl acetate as an eluent, concentrated, dissolved in chloroform, filtered, and concentrated to give 7.9 mg (100%) of the desired compound as a white solid. Mass spectrum: $(M+H)^+$ = 714.

Example 288

Boc-Phe-His amide of (2S,3S,5S)-N-isobutyl-2-amino-1-cyclohexyl-7-methyloctane-3,5-diol-5-carboxamide

Using the procedure of Example 283 with the resultant compound of Example 276 gave, after purification by flash column chromatography using 6% methanol in chloroform, an 85% yield of the desired compound (R_f .16; 7.5% methanol in chloroform). Mass spectrum: $(M+H)^+$ = 741.

97-99°C. Mass spectrum: $(M+H)^+$ = 548.

Example 293

His amide of (4S,5S)-N-(3-methylbutyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide dihydrochloride

Using the procedure of Example 272 with the resultant compound of Example 292 gave the desired compound.

Example 294

Boc-6-aminohexanoic acid

A mixture of 3.0 g (0.02 mol) of 6-aminohexanoic acid, 5.04 g (0.02 mol) of di-t-butyldicarbonate and 3.84 g (0.05 mol) of $NaHCO_3$ in 160 ml of 1:1 H_2O/tetrahydrofuran was stirred vigorously for 24 h. After concentration of the solvent, the mixture was acidified with HCl, saturated with NaCl, extracted with ethyl acetate, dried over $MgSO_4$ and concentrated in vacuo to give the desired product (R_f 0.48, 9:1 chloroform/methanol).

Example 295

Boc-6-aminohexanoyl-Phe benzyl ester

A solution of 1.50 g (6.5 mmol) of the resultant compound of Example 294, 2.77 g (6.5 mmol) of phenylalanine benzyl ester p-toluenesulfonate salt, 0.87 g (6.5 mmol) of 1-hydroxybenzotriazole hydrate, 1.19 ml (8.4 mmol) of triethylamine and 1.74 g (8.4 mmol) of dicyclohexylcarbodiimide in 150 ml of tetrahydrofuran was allowed to stir at ambient temperature for 18 h. After concentration in vacuo, the residue was taken up in 300 ml of ethyl acetate, filtered, washed consecutively with 1 M HCl, H_2O, saturated $NaHCO_3$, H_2O and saturated NaCl; dried over $MgSO_4$ and concentrated. Purification by flash column chromatography using 4:1 chloroform/ethyl acetate gave 2.35 g (77%) of the desired compound (R_f 0.21, 4:1 chloroform/ethyl acetate).

purification by flash column chromatography using 7.5% methanol in chloroform, a 32% yield of the desired compound as a mixture of diastereomers (R_f .09, .11, 7.5% methanol in chloroform). Mass spectrum: $(M+H)^+$ = 808.

Example 300

(5N)-t-Butylacetyl-Phe-His amide of N-(3-amino-2,2-dimethylpropyl)-5-amino-6-cyclohexylhex-1-en-4-ol-2-carboxamide

Using the procedure of Example 272 with the resultant compound of Example 299 gave a white solid. Purification and neutralization by flash column chromatography using 7.5-10% methanol/2% isopropylamine in chloroform gave a 38% yield of the desired compound (R_f .29, 10% methanol/2% isopropylamine in chloroform). Mass spectrum: $(M+H)^+$ = 708.

Example 301

(4S,5S,8R,10R,11S)-N-Isobutyl-6-aza-11-(t-butyloxycarbonylamino)-5-(cyclohexylmethyl)-4,10-dihydroxy-8-isobutyl-7-oxo-12-phenyldodec-1-ene-2-carboxamide

Using the procedure of Evans, et al. (J. Org. Chem. 1985, 50, 4615) with the resultant compound of Example 270 and (3R,5R,1'S)-5-(1-(t-butyloxycarbonylamino)-2-phenylethyl)-3-isobutyldihydrofuran-2-(3H)-one (D.J. Kempf, J. Org. Chem. 1986, 51, 3921) gave the desired compound after purification by column chromatography using 3:2 ethyl acetate:hexane. Mass spectrum: $(M+H)^+$ = 658.

Example 302

(4S,5S,8R,10S,11S)-N-Isobutyl-6-aza-11-(t-butyloxycarbonylamino)-5-(cyclohexylmethyl)-4,10-dihydroxy-7-oxo-8-(4-pentenyl)-12-phenyl-dodec-1-ene-2-carboxamide

Using the procedure of Evans, et al. (J. Org. Chem. 1985, 50, 4615) with the resultant compound of

Example 306

5-Carbomethoxypentanoyl-(O-methyl)Tyr benzyl ester

Using the procedure of Example 280 but replacing Boc-Phe-Ala-OH with adipic acid monomethyl ester and replacing the resultant compound of Example 269 with (O-methyl)tyrosine benzyl ester hydrochloride gave the desired compound.

Example 307

5-Carbomethoxypentanoyl-(O-methyl)Tyr-OH

A solution of the resultant compound of Example 306 and 20% palladium on carbon in methanol was shaken under an H_2 atmosphere. After filtration, concentration of the solution in vacuo gave the desired compound.

Example 308

5-Carbomethoxypentanoyl-(O-methyl)Tyr-Leu benzyl ester

Using the procedure of Example 280 but replacing Boc-Phe-Ala-OH with the resultant compound of Example 307 and replacing the resultant compound of Example 269 with leucine benzyl ester p-toluenesulfonate salt gave, after purification by flash column chromatography using 20% ethyl acetate in chloroform, the desired compound in 64% yield.

Example 309

5-Carbomethoxypentanoyl-(O-methyl)Tyr-Leu-OH

A solution of the resultant compound of Example 308 and 20% palladium on carbon in methanol was shaken under an H_2 atmosphere. After filtration, concentration of the solution in vacuo gave the desired compound in 97% yield.

Example 310

5-Carbomethoxypentanoyl-(O-methyl)Tyr-Leu amide of N-(2,2-dimethyl-3-(N,N-dimethylamino)propyl)-5-amino-4-hydroxy-6-cyclohexylhex-1-ene-2-carboxamide

Using the procedure of Example 280 but replacing Boc-Phe-Ala-OH with the resultant compound of Example 309 and replacing the resultant compound of

Mass spectrum: $M^+ = 379$.

Example 313

4(S)-t-butyloxycarbonylamino-2,2-difluoro-3R-hydroxy-5-cyclohexylpentanoic acid.

Using the procedure of Example 156, but replacing Boc-Sta-OEt with the product from Example 312 gave the desired product. Mass spectrum: $M^+ = 351$.

Example 314

4S-t-butyloxycarbonylamino-2,2-difluro-3R-hydroxy-5-cyclohexylpentanoic acid amide of 2-methylbutylamine.

Using the procedure of Example 157, but replacing Boc-Sta-OH with the product from Example 313 and replacing benzyl amine with 2-methylbutylamine gave the desired product (75% yield). Mass spectrum: $M^+ = 420$.

Example 315

Boc-Phe-His-4S-amino-2,2-difluoro-3R-hydroxy-5-cyclohexylpentanoic acid amide of 2-methylbutylamine.

Using the procedure of Example 164, but using the amine hydrochloride of the product in Example 314 gave the desired product (47% yield). Mass spectrum: $(M+H)^+ = 705$.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, citrate, camphorate, camphorsulfonate, cyclopentanepropionate, digluconate, dodecylsulfate, ethanesulfonate, fumarate, glucoheptanoate, heptonate, glycerophosphate, hemisulfate, hexanoate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, oxalate, 2-naphthalenesulfonate, pamoate, pectinate, persulfate,

specific dose level for any particular patient will depend upon a variety of factors including the activity of the specific compound employed, the age, body weight, general health, sex, diet, time of administration, route of administration, rate of excretion, drug combination, and the severity of the particular disease undergoing therapy.

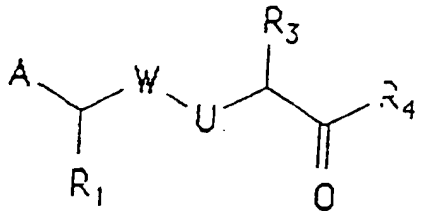
The compounds of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

Injectable preparation, for example, sterile injectable aqueous or oleagenous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

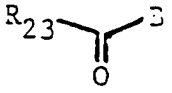
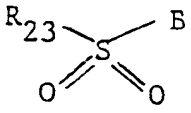
Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and

WHAT IS CLAIMED IS:

1. Compounds of the formula



wherein A is hydrogen; loweralkyl; arylalkyl; OR_{20} or SR_{20} wherein R_{20} is hydrogen, loweralkyl or aminoalkyl; $NR_{21}R_{22}$ wherein R_{21} and R_{22} are independently selected from hydrogen, loweralkyl, aminoalkyl, cyanoalkyl and hydroxyalkyl;

 and 

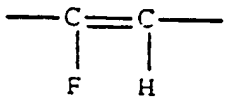
wherein B is NH, alkylamino, S, O, CH_2, $NHCH_2$ or CHOH and R_{23} is loweralkyl, cycloalkyl, aryl, arylalkyl, alkoxy, alkenyloxy, hydroxyalkoxy, dihydroxyalkoxy, arylalkoxy, arylalkoxyalkyl, amino, alkylamino, dialkylamino, (hydroxyalkyl)(alkyl)amino, [(dialkylamino)alkyl](alkyl)amino, (dihydroxyalkyl)(alkyl)amino, carboxyalkyl, aminoalkyl, N-protected aminoalkyl, alkylaminoalkyl, alkoxycarbonylalkyl, (N-protected)(alkyl)aminoalkyl, dialkylaminoalkyl, (heterocyclic)alkyl or a substituted or unsubstituted heterocyclic;

W is C=O or CHOH;

U is CH_2 or NR_2, provided that when W is CHOH then U is CH_2;

R_1 is loweralkyl, cycloalkylmethyl, benzyl, 4-methoxybenzyl, halobenzyl, (1-naphthyl)methyl, (2-naphthyl)methyl, (4-imidazoyl)methyl, 4-hydroxybenzyl, α,α-dimethylbenzyl, 1-benzyloxyethyl,

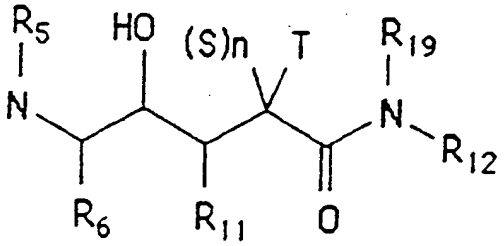
wherein R_5 is hydrogen or loweralkyl; R_6 is loweralkyl, cycloalkylmethyl, benzyl, or CH_2R_{24}, where R_{24} is selected from 1,3-dioxan-2-yl; 1,3-dioxolan-2-yl, 1,3-dithiolan-2-yl or 1,3-dithian-2-yl; R_7, R_8 and R_9 are hydrogen or loweralkyl and may be the same or different; V is NH, O, S, SO, SO_2, or CH_2; R_{10} is loweralkyl, cycloalkyl, cycloalkyl-alkyl, aryl, arylalkyl or an N-protecting group, or V and R_{10} taken together are N_3; with the proviso that R_{10} may be an N-protecting group only when V is NH; R_{13} is CHOH or CO; R_{14} is CH_2, CF_2 or CF with the proviso that when R_{13} is CO, R_{14} is CF_2; R_{15} is CH_2, CHR_{25} wherein R_{25} is loweralkyl, cycloalkyl, cycloalkylalkyl, aryl or arylalkyl, or R_{14} and R_{15} taken together can be



with the proviso that when R_{14} is CF_2, R_{15} is CH_2; M is O, S, SO, SO_2, NR_{26} wherein R_{26} is hydrogen or loweralkyl, $NR_{27}SO_2$ or $NR_{27}CO$ wherein R_{27} is hydrogen or loweralkyl, or M and R_{10} taken together are N_3; R_{16} is CH_2, CF_2 or CHR_{45} where R_{45} is loweralkyl, hydroxy, hydroxyalkyl, alkoxy, allyl, alkaryloxy or thioalkyl R_{17} is hydrogen or loweralkyl; R_{18} is loweralkyl or lipophilic or aromatic amino acid side chains; P is hydrogen, loweralkyl or $-CH_2OR_{28}$, wherein R_{28} is hydrogen, loweralkyl or alkaryl; R_{11} is hydrogen or hydroxy; n is 0 or 1; when n is O, T is alkylidene or alkylidene oxide; when n is 1, S is hydrogen or hydroxy and T is loweralkyl, hydroxyalkyl, aminoalkyl, haloalkyl, or azidoalkyl; R_{19} is hydrogen or loweralkyl; R_{12} is hydrogen, loweralkyl, alkyl- cycloalkyl, arylalkyl,

and R_1 is 1- or 2-naphthylmethyl, benzyl or 4-methoxybenzyl; R_3 is loweralkyl, imidazol-4-yl-methyl, pyrazolylmethyl, or thiomethoxymethyl; R_5, R_{17} is hydrogen; R_{16} is CH_2; R_6 is isobutyl, cyclohexylmethyl or CH_2R_{24}, where R_{24} is 1,3-dithiolan-2-yl; P is hydrogen or hydroxymethyl; and R_{18} is loweralkyl.

5. A compound according to Claim 1 wherein R_4 is



and R_1 is 1- or 2-naphthylmethyl, benzyl or 4-methoxybenzyl; R_3 is loweralkyl, imidazol-4-yl-methyl, pyrazolylmethyl, or thiomethoxymethyl; R_5, R_{11} and R_{19} are hydrogen; R_6 is isobutyl or cyclohexylmethyl; and R_{12} is loweralkyl, aminoalkyl or dialkylaminoalkyl.

6. A compound according to Claim 2 wherein A is (morpholin-4-yl)carbonyl-CH_2; R_1 is benzyl; W is carbonyl; U is NH; R_3 is (imidazol-4-yl)methyl; R_6 is cyclohexylmethyl; V is SO_2 and R_{10} is isopropyl.

7. A compound according to Claim 2 wherein A is BocNH; R_1 is benzyl; W is carbonyl; U is NH; R_3 is (imidazol-4-yl)methyl; R_6 is cyclohexylmethyl; V is CH_2 and R_{10} is isopropyl.

8. A compound according to Claim 3 wherein A is BocNH; R_1 is benzyl; W is carbonyl; U is NH; R_3 is isobutyl; R_6 is cyclohexylmethyl; R_{13} is C=O, R_{14} is CF_2; M is SO_2 and R_{10} is isopropyl.

9. A compound according to Claim 3 wherein A is BocNH; R_1 is benzyl; W is carbonyl; U is NH; R_3 is pyrazol-3-ylmethyl; R_6 is cyclohexylmethyl; R_{13} is

INTERNATIONAL SEARCH REPORT

International Application No PCT/US87/00054

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all) [3]

According to International Patent Classification (IPC) or to both National Classification and IPC

US. CL. 514/17,18,19; 530/329,330,331
INT. CL. -4- A61K 37/43; CO7K 5/06,08,10; Co7K 7/06

II. FIELDS SEARCHED

Minimum Documentation Searched [4]

Classification System	Classification Symbols
US	514/17,18,19; 530/329,330,331

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched [5]

III. DOCUMENTS CONSIDERED TO BE RELEVANT [14]

Category *	Citation of Document, [16] with indication, where appropriate, of the relevant passages [17]	Relevant to Claim No. [18]
P,X	Chemical Abstract, Vol. 104, Issued 1986 abstract no. 88976x, (Matsueda)	1-14
P,X,	Chemical Abstract, Vol. 105, Issued 1986 abstract no. 43336t, (Luly)	1-14
P,X,	Chemical Abstract, Vol. 105, Issued 1986 abstract no. 433377u, (Luly)	1-14
P,X,	Chemical Abstract, Vol. 105, Issued 1986 abstract no. 24630, (Boger)	1-14
P,X,	Chemical Abstract, Vol. 105, Issued 1986 abstract no. 79375u, (Ryono)	1-14
P,X,	Chemical Abstract, Vol. 105, Issued 1986 abstract no. 60945h, (Fuhrer)	1-14
P,X,	Chemical Abstract, Vol. 105, Issued 1986 abstract no. 153525, (Thaisrivongs)	1-14
P,X,	Chemical Abstract, Vol. 105, Issued 1986 abstract no. 153529r, (Thaisrivongs)	1-14

* Special categories of cited documents: [15]

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search [2]	Date of Mailing of this International Search Report [2]
17 March 1987	20 MAR 1987
International Searching Authority [1]	**Signature of Authorized Officer [20]**
ISA/US	

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category *	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No
X	Chemical Abstract, Vol. 102, Issued 1985, abstract no. 181341, (Gelb)	1-14
X,	Chemical Abstract, Vol. 103, Issued 1985, abstract no. 160849, (Thaisrivongs)	1-14
X	Chemical Abstract, Vol. 103, Issued 1985, abstract no. 54459, (Szeke)	1-14
X,	Chemical Abstracy, Vol. 104, Issued 1986, abstract no. 162094b, (Dann)	1-14
A,	Chemical Abstract, Vol 104, Issued 1986, abstract no. 149414, (Boger)	1-14
P,X,	Chemical Abstract, Vol. 104, Issued 1986, abstract no. 149418, (Boger)	1-14